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PRESENT TRENDS IN THE STUDY OF ARTHRITIS AND RHEUMATISM*

RUSSELL L. CECIL, M.D.
New York, N. Y.

RHEUMATOID arthritis and rheumatic fever constitute two of the last remaining unsolved problems in the field of the infectious diseases. For this reason they possess exceptional fascination to the investigator, so much so that today a small-sized army of bacteriologists, physiologists and chemists are attempting to dispel the mystery which still surrounds the etiology of these conditions. It must not be inferred, however, that when we call the arthritis problem unsolved we mean to deny the progress which is being made every year in our knowledge and understanding of the disease. If we must admit that the etiology of rheumatoid arthritis and rheumatic fever is still unknown, we may add, in the same breath, that recent investigations are throwing more and more light into this dark corner of medicine and that there is good reason to believe that within another decade, students of rheumatism will have a much clearer conception of the pathogenesis of these two great diseases than we have today.

In the present discussion I propose to touch only the high spots of recent research and will exercise the prerogative of every investigator in dwelling especially on those phases of the problem which have been studied in our own laboratories at the Cornell Medical College.

First let us discuss a very fundamental aspect of the problem, namely terminology and classification. Students of arthritis are beginning to demand more accurate criteria for the identification of the various forms of arthritis. This is particularly so of rheumatoid arthritis, a disease which has been very much abused so far as terminology is concerned. In the past, vague and desultory joint pains of all kinds have been casually glorified by the designation of rheumatoid arthritis. So many young physicians who have had no training or background in morbid anatomy fail to realize that rheumatoid arthritis is a very definite disease entity, characterized by well defined pathological changes in the joints and in the subcutaneous tissue when nodules are present, and that unless some of the genuine features of the disease are present, the diagnosis of rheumatoid arthritis should never be made. Such carelessness in terminology is particularly unfortunate when clinical reports of some form of therapy are being made. If one includes under rheumatoid arthritis the various arthralgias and psychoneuroses that one sees so frequently in arthritis clincs, the statistical value of the report from the therapeutic standpoint is completely nullified. In my clinic I am constantly being surprised by some of the conditions which are filed under rheumatoid arthritis. For example, osteoarthritis may be mistakenly classified under rheumatoid arthritis, just because the patient shows a high sedimentation rate. The arthralgias of menopause are frequently termed rheumatoid.

The New York City Committee on Arthritis Clinics has been working this winter on a classification of arthritis, and the classification shown in Table I, though provisional, seems to me to be as satisfactory as any.

Briefly I should say that the clinical criteria for the diagnosis of rheumatoid arthritis would be the following:

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(1) Some of the joints must be swollen, and preferably some one or more of the knuckles or the proximal interphalangeal joints of the fingers.

(2) The disease is practically always polyarticular and tends to remain in the joints already involved as it spreads to new joints.

(3) There is a strong tendency to symmetrical distribution of the affected joints. In my opinion the typical fusiform finger is the most characteristic feature of the disease. I always hesitate to make a diagnosis of rheumatoid arthritis when the swelling of the hand and fingers is of a diffuse character.

(4) There is usually evidence of general systemic infection, as indicated by slight fever, anemia, and loss of weight and strength. The vasomotor disturbances are quite characteristic, especially excessive perspiration and rapid wasting of the muscles.

(5) The sedimentation rate of the red cells is practically always increased quite markedly.

(6) The x-ray appearance of the bones and joints is highly characteristic. One of the earliest changes is the osteoporosis of the bones adjacent to the affected joints. As the disease progresses, there is narrowing of the interarticular space and blurring of the whole joint architecture. Small punched-out areas are sometimes seen about the head of the bone adjacent to the affected joint.

(7) The agglutination test with the patient's serum against the streptococcus hemolyticus is positive in 65 to 75 per cent of cases.

(8) In well established cases of several years duration, characteristic ankylosis and deformity of the affected joints renders the diagnosis very simple.

Pathology of Rheumatoid Arthritis.—In 1929 A. G. Timbrell Fisher[23] pointed out certain microscopic features in the synovial membrane in rheumatoid arthritis. He particularly stressed the numerous agglomerations of small round cells which form rounded masses in the region of the blood vessels. In 1931 Allison and Ghormley[2] published a monograph on arthritis in which they stressed still more strongly the presence of focal collections of lymphoid cells in the synovial membrane. To quote these writers: "Histologically the tissues show a definite picture, which is as clear cut as is that of tuberculosis, namely a proliferative change in the synovial membrane and marrow which is characterized by focal collections of lymphocytes. This microscopic picture will, we believe, be enough to establish the diagnosis of proliferative (rheumatoid) arthritis." It is true that these collections of lymphoid cells are nearly always present in the synovial membrane of the affected joint in rheumatoid arthritis. Furthermore, in a recent study from our laboratory, in collaboration with Angevine and Rothbard,[9] we were able to produce an experimental hemolytic streptococcus arthritis in rabbits which presented a picture very similar to that described by Allison and Ghormley. In other words, the same collections of lymphoid cells were found in the synovial membrane of the rabbit as were found in human tissue. However, further experiments showed that a similar picture could be produced in experimental pneumococcus arthritis, and Jordan[32] has recently shown that when turpentine is injected into the synovial tissue of rabbits, a lesion can be produced which is indistinguishable from the experimental streptococcal arthritis and quite similar to that seen in human rheumatoid arthritis.

Interesting reports have appeared in recent years on the pathology of subcutaneous nodules in rheumatoid arthritis and rheumatic fever. Here again we encounter peculiar agglomerations of cells about central areas of necrosis which are not seen in any other disease. However, Dawson[17] has shown that the histopathology of the subcutaneous nodule of rheumatoid arthritis differs little, if any, from that of the subcutaneous nodule of rheumatic fever.

Summarizing then, we may say that the synovial membrane and the subcutaneous nodules in rheumatoid arthritis presents interesting and characteristic histological changes, but that these changes are not absolutely specific for rheumatoid arthritis.

Etiology of Rheumatoid Arthritis.—It must be admitted that the theory of focal infection, so popular a few years ago, is very much on the wane in so far as it applies to the etiology of rheumatoid arthritis. The theory of focal infection was first invoked by Frank Billings[7] as an explanation for the pathogenesis of rheumatoid arthritis. However, if one goes back to Billings' original article and reviews the ten

cases on which his study was based, it is at once evident that some of them today would not be classified as typical rheumatoid cases. Not only Billings, but most of the earlier writers on arthritis, failed to differentiate clearly between infectious and rheumatoid forms. However, the most significant feature of this problem is the fact that while foci of infection were being rapidly disposed of, rheumatoid arthritis remained as prevalent as ever. Two years ago we were so impressed with this fact that Dr. Angevine and I[8] analyzed 200 cases of rheumatoid arthritis with special reference to the incidence of focal infection. In analyzing these carefully studied cases, we found definite evidence of infection in only 20 per cent of the series, and a questionable focus in 10 per cent. We were surprised to find that 70 per cent of the patients revealed no demonstrable focus of infection. But this was not all. Even when foci of infection were present, their removal seemed to have no permanent beneficial effect on the course of the disease. For example, tonsillectomy had no influence on the disease in eighty-eight cases, and caused a severe exacerbation of the disease in two instances. In no case was the course of the disease arrested or the patient cured. Extraction of the teeth gave no benefit in forty-seven cases, and three patients reported a flare-up of pain in their joints following teeth extraction. The results following drainage of infected sinuses were quite ineffective. As a result of our study, we concluded that internists must exercise a more conservative attitude regarding infected tonsils, sinuses and teeth than they have in the past, and not leave a decision regarding the treatment of these so-called foci to specialists. Evidently the time has arrived for a complete revaluation of the focal infection theory. Focal infection undoubtedly plays an important part in a number of ailments, and we were convinced from our study that there is a type of infectious arthritis, not rheumatoid in character, which is related to focal infection and which is benefited by the removal of infected foci. In this type of arthritis one or more large joints are affected. The patient runs a fever and the picture is not unlike that of rheumatic fever. However, the symptoms do not yield to salicylates and there are no cardiac complications.

TABLE I—CLASSIFICATION OF ARTHRITIS

I. Infectional Arthritis
   (a) Of proved etiology.
II. Probably Infectional; etiology unproved.
   (a) Arthritis of rheumatic fever.
   (b) Rheumatoid arthritis (atrophic arthritis; chronic infectious arthritis)
      1. Adult type.
      2. Juvenile type (Still's disease)
      3. Ankylosing spondylitis (Marie-Strumpell)
      4. Psoriatic arthritis.
   (c) Arthritis associated with various infections.
III. Degenerative arthritis (osteoarthritis; hypertrophic arthritis)
   (a) Generalized; etiology unknown.
   (b) Localized.
      1. Secondary to trauma.
      2. Secondary to structural abnormality.
      3. Secondary to previous infectional arthritis.
      4. Etiology unknown.
IV. Arthritis associated with disturbance of metabolism.
   (a) Gout.
   (b) Arthritis manifestations of other metabolic diseases.
V. Arthritis of Neuropathic origin.
   (a) Secondary to tabes dorsalis.
   (b) Secondary to syringomyelia.
   (c) Secondary to peripheral nerve lesions.
VI. Miscellaneous forms.
   (a) Arthritis of serum sickness.
   (b) Arthritis of hemophilia.
   (c) Intermittent hydra-arthrosis.

Bacteriology of Rheumatoid Arthritis.—The earlier students of focal infection, particularly Rosenow[38] and his co-workers, emphasized the frequency with which streptococci were recovered from focal infections and from this they made the inference that rheumatoid arthritis was probably a streptococcal disease. This theory has enjoyed wide popularity for years. In 1929 the writer, in collaboration with Nicholls and Stainsby[10] undertook a detailed study of the bacteriology of the blood and joints in patients with rheumatoid arthritis. By using a special culture method, streptococci were recovered from the blood in 62 per cent and from the joints in 67 per cent of 154 patients with rheumatoid disease. Most of the strains recovered in this series were attenuated streptococci. Control cultures on other normal individuals or patients suffering from other diseases yielded negative results. This work was repeated in

numerous laboratories with variable results, some confirming, others failing to confirm these observations. However, in the majority of instances, negative results were obtained. More recently Dr. Angevine and Dr. Steffen have endeavored to repeat the work of Nicholls and Stainsby, but their results have been entirely negative. As a result of these negative findings, one is forced to suspect that the streptococci recovered in earlier studies were contaminations, but this of course can not be absolutely proven.

In 1931, Cecil, Nicholls and Stansby[12] first noted the presence of specific agglutinins for the streptococcus hemolyticus in the sera of patients with rheumatoid arthritis. In a series of 103 cases of this disease, ninety-seven showed agglutination with the hemolytic streptococcus at a dilution of 1:640 or higher, while in a series of fifty normal controls, the serum in every case failed to give a strong agglutination reaction. The presence of these agglutinins has been confirmed by Dawson, Olmstead and Boots[18] and a number of other investigators. The percentage of patients showing a postive reaction has varied according to different observers from 40 to 90 per cent. In the opinion of the writer, the percentage of cases showing this positive reaction will depend on the duration and severity of the disease. In well-established cases of several years duration and with active swelling of many joints, the percentage of positive reactions should be about 90 per cent. If all patients, including incipient cases, are included, the percentage of positive reactions will run between 55 and 60 per cent.

It was interesting to observe that the agglutination reaction is often strongly positive in patients whose cultures fail to reveal hemolytic streptococci, and this statement applies not only to blood and joint cultures, but to cultures from the throat, stools, etc. Because of this fact the question has been raised as to whether this is a truly specific agglutination reaction or a nonspecific phenomena similar to the Felix-Weil agglutination of the proteus bacillus by the serum of patients with typhus fever. In the last year or so bacteriologists have shifted their interest from the streptococcus group of organisms to the so-called pleuropneumonia-like group. These peculiar micro-organisms are very tiny, varying from .5 u down to 0.2 u or less in diameter. From such granules slender threads may grow out, which form a single filament, or they may bud out from several parts of the granule to form delicate star-shaped structures. These threads become branched and form a dense mycelial-like network. About the margins of the colonies the threads become enlarged to form coarse globular or club-shaped bodies. These organisms have been found to exist in symbiosis with the Streptobacillus moniliformis, the organism which Klieneberger[33] frequently obtained by inoculating mice with the pharyngeal exudate of rats. Recently Findlay[22] and his co-workers have cultivated the pleuropneumonia-like organism from the joint tissue of rats suffering from a type of polyarthritis. They were able to reproduce the disease in mice by injecting into the foot pads filtered or unfiltered suspensions of joint tissue, or cultures grown from them, along with a bit of agar. Sabin[39] has also produced a chronic arthritis in mice by intravenous or intraperitoneal injections of cultures of the strain he isolated from the brain of a normal mouse. He described this as a progressive, proliferative polyarthritis, resembling rheumatoid arthritis in man. The process often goes on to ankylosis of one or more joints. Sabin was able to recover the organism in cultures from the joints as late as seventy days after inoculation by blind passages, that is, by a series of subcultures repeated at short intervals without waiting for evidence of growth to appear.

Another interesting etiological theory which has received considerable attention has to do with the role of vitamin deficiency in rheumatoid arthritis. This applies particularly to the studies of Rinehart[37] in relation to vitamin C deficiency. Rinehart found that chronic vitamin C deficiency in the guinea pig produces an arthropathy with many similarities to rheumatoid arthritis, and that in certain instances superimposed infection accelerates and accentuates the pathological process. In Rinehart's study on guinea-pigs the experimental infection, in the presence of adequate vitamin C, failed to produce arthritis. Rinehart points out that the general atrophic changes in rheumatoid arthritis, involving the bony skeleton, muscle and skin, are seen also in chronic vitamin C deficiency. Rinehart concludes that vitamin C deficiency may operate as a factor in the etiology of rheumatoid arthritis. It must be admitted that Rine-

hart has presented an intriguing theory, but one which does not receive much support from practical experience. In other words, there is very little clinical evidence to support the idea that patients with rheumatoid arthritis are suffering from a deficiency of vitamin C, and certainly vitamin C in large doses does not cure the disease.

Psychic Shock.—Several interesting articles have appeared recently on the relation of psychic trauma to the onset and recrudescence of rheumatoid arthritis. It seems quite likely that this is merely a predisposing cause, but the fact remains that a good many patients trace the onset of their disease to a psychic shock and many others give a history of some emotional disturbance preceding relapse. Cobb, Bauer and Whiting[13] made a careful study on the relationship between the onset of exacerbations of arthritis and the emotional or environmental factors, and found that environmental stress, especially poverty, grief and family worry seem to bear a definite relationship to the onset of exacerbations of rheumatoid arthritis.

Treatment of Rheumatoid Arthritis.—The therapy of rheumatoid arthritis continues to be empirical, with new cures constantly coming in and going out. A revival of sulphur therapy has been attempted on the theory that the cells of an arthritic patient have lost the ability to retain sulphur. Sullivan and Hess,[42] for example, expressed the belief that the cystine content of the finger nails of arthritic patients is definitely low, an indication of disturbed metabolism of sulphur. Freyberg,[25] however, has taken issue with this theory and has shown pretty clearly that the sulphur metabolism in arthritis is entirely normal.

So far as treatment of rheumatoid arthritis by medication is concerned, gold salts are now attracting the greatest interest. Gold therapy for arthritis was first instituted twelve years ago by Forestier.[24] It soon became quite popular in Europe, but was disregarded almost entirely by American students until quite recently. The mode of action of gold in arthritis is unknown. Intramuscular injections seem to be quite as effective as intravenous injections, and are probably safer. The drug is given in courses in much the same way as bismuth and arsphenamin in syphilis. The usual method of treatment is to begin with 25 to 50 milligrams, and work the dose up to 100 milligrams. There is some difference of opinion as to what constitutes a course, but most authorities advise a total dosage of 1 to 2 grams, depending on how the patient reacts to the drug. Injections are usually given once a week, deep into the buttock with a long needle. Most writers recommend several courses, believing that relapses and failures result when only one course is administered. Patients on gold therapy should be followed with frequent blood counts, urinalyses and sedimentation tests.

Of the number of different gold products on the market, the most popular ones in this country are sodium gold thiosulfate, Solgonol B, and Myochrysine. Reactions to gold are numerous and some of these may be quite serious. Occasionally fatal results have been noted. Many patients have an immediate vasomotor disturbance, which is not serious but unpleasant, following the injection. Undoubtedly the commonest form of toxic reaction is drug dermatitis, which appears as a dry scaly itching erythema or morbiliform rash. Occasionally severe exfoliative dermatitis is encountered. Next to dermatitis, the writer has found stomatitis the commonest toxic manifestation, showing itself as a loss of taste, sore tongue and gums, or an ulcerative stomatitis. A few patients develop acute gastro-intestinal symptoms with fever, vomiting, epigastric pain and diarrhea. Occasionally acute hepatitis with jaundice is encountered, and rarely acute yellow atrophy. Occasional instances of glomerular nephritis occur, and finally purpura hemorrhagica, aplastic anemia and agranulocytosis. While exfoliative dermatitis is extremely unpleasant and may occasionally be serious, it is the disturbances of the hematopoietic system which are the most to be feared. Some observers believe that the toxic manifestations of gold therapy can be avoided by simultaneous injection of calcium gluconate; others recommend liver extract or glucose.

In spite of the dangers attendant to gold therapy, most investigators who have had extensive experience with the gold salts are quite enthusiastic over the results obtained. Hartfall and Garland[29] saw results which were little short of miraculous on patients showing various grades of disability. They also noted improved

general health and appetite, gain in weight and reduction in sedimentation rate. The writer has now treated over 200 cases of rheumatoid arthritis with gold therapy. Unfortunately time has not been yet available for a careful analysis of these figures. Like many others, my earlier experiences with gold were discouraging. A severe case of exfoliative dermatitis was encountered quite early, and this engendered a fear of the drug which prevented adequate dosage being administered to other patients. With increasing experience, however, I came to place a high value on gold, particularly Myochrysine, with which I have done most of my work. I have encountered no serious disturbances in the blood. There have been three cases of exfoliative dermatitis; two have been quite severe. I have seen a few quite remarkable recoveries and many others that were striking, particularly when the drug was administered early in the disease. In conclusion, I think it is fair to say that gold therapy marks an important advance in the treatment of rheumatoid arthritis. It is a dangerous agent, but in the hands of an experienced therapist it can be used with great benefit in the treatment of rheumatoid patients. Perhaps the greatest objection to the drug is that a good many patients simply cannot take it without developing a skin rash. With the development of dermatitis, of course, the drug has to be discontinued, sometimes only temporarily, at other times permanently.

Vaccine therapy is still popular in many arthritis clinics, but has lost some of its vogue because of the growing popularity of gold therapy. However, in the writer's opinion, streptococcus vaccine still has a place in the treatment of rheumatoid arthritis. In our clinic we use it on those patients who cannot take gold, and occasionally it is used in combination with gold.

Fever therapy has been extensively tried and there are now numerous reports in the literature. The results are fairly consistent. The majority of the patients receive relief from fever therapy, but in most cases this benefit is only temporary. However, there remains about 10 per cent of patients who are really greatly benefited by fever therapy. These are usually early cases, and in such patients I am always tempted to try fever therapy at least once or twice, just to discover how they react to treatment.

Vitamins have become an integral part of the routine therapy of rheumatoid arthritis, most of the physicians giving generous quantities of A, B, C and D to arthritic patients. I have already referred to Rinehart's studies on vitamin C in relation to rheumatoid arthritis, though of particular interest is the work of Dreyer and Reed,[19] who strongly advocate massive daily doses of vitamin D for the treatment of rheumatoid arthritis. The doses recommended of 200 to 250 thousand U. S. P. units a day frequently excite toxic symptoms, chiefly nausea, anorexia, lassitude, diarrhea and severe gastrointestinal pain. Some writers, notably Irons,[3] offer objections to this massive vitamin D therapy on the plea that some permanent injury might be done by such doses. Massive vitamin D therapy has not met with an enthusiastic response from the profession. Slocum and Hench[41] were unable to obtain any benefit from this therapy on twenty-five rheumatoid patients, and similar negative results have been reported by Bauer.[1] The writer's own personal experience has also been disappointing.

A word must be said here about the studies of Hench[30] on the relation of jaundice to rheumatoid arthritis, and its application in the use of bile salts. It has been known for some time that an attack of catarrhal obstructive jaundice would produce a remarkable amelioration in the symptoms of rheumatoid arthritis. Hench[30] studied thirty-one cases of atrophic arthritis and fibrositis in relation to jaundice. In most instances the jaundice was caused by the toxic action of cinchophen, but the patients who had simple catarrhal jaundice expressed similar relief. In the majority of cases, marked reduction of pain and swelling and a striking increase in motion accompanied the more or less complete analgesia, and the rheumatic process appeared to have suddenly become inactive for varying periods, sometimes only for days or weeks, occasionally for months or years. Only a few weeks ago the writer had an opportunity to study one of these cases at close range. A young woman, aged twenty-four, with typical rheumatoid arthritis of four years duration, was put on gold therapy. After she had had about ten injections of Sanochrysine, she developed a toxic hepatitis with headache, jaundice and bile-stained urine. The jaundice appeared about two months after the last injec-

tion of gold and lasted four to five weeks. Previous to the onset of the jaundice, she had considerable arthritis in various joints, with swollen wrists and ankles, several fusiform fingers and swelling of the right knee. Within a week or so after the onset of jaundice, the swelling and pain disappeared entirely from her joints and there was complete restoration of function. This period of inactivity lasted three months, when the symptoms in her joints gradually returned to the state they had been in previous to the attack of jaundice. These observations on jaundice and its effect on rheumatoid arthritis has led to the administration of bile salts to patients with this disease. Thompson and Wyatt[47] employed bile salts alone and bilirubin alone without any beneficial effect. However, the *combination* of bilirubin and bile salts seemed to have a favorable influence on the symptoms. Hench,[30] however, was unable to confirm these observations. Margolis[35] has employed autolyzed liver which, in his experience, produced exacerbation of the symptoms. Davis,[16] working in our Department of Physiology at Cornell, believes that crude liver extract, when given in large doses, has a favorable effect on the course of arthritis, but I have not been able to confirm this observation on a very limited number of cases. Everyone seems to be agreed that jaundice, either natural or experimental, is not a cure for arthritis, but is only a temporary palliative.

Rheumatic Fever

Coming now to the subject of rheumatic fever, we find a situation quite similar in many respects to that which exists in rheumatoid arthritis, particularly in so far as studies on etiology are concerned. The disease is still classified as probably infectious, though of unknown origin, and the weight of opinion still favors the hemolytic streptococcus as the causative agent. The reasons for this opinion are obvious enough and have been particularly stressed by Coburn[15] and others in their studies on the relation of rheumatic fever to acute respiratory infections.

Green[27] has recently cultured the throat of patients with acute rheumatic fever and compared his results with cultures from nonrheumatic controls. Hemolytic streptococci were recovered in 58 per cent of the rheumatic cases and from only 30 per cent of the nonrheumatic cases. More recently Green[28] claims to have actually recovered hemolytic streptococci from cardiac vegetations of patients dying of rheumatic fever. We have not been able to corroborate this work, however, in our own investigations. A decade ago the writer, in collaboration with Nicholls and Stainsby,[11] recovered streptococci of various types from the blood and joints of patients with acute rheumatic fever. These results, however, have not been confirmed by recent studies in our laboratory and the previous findings are therefore open to the same criticism that has been made of the positive cultures obtained in rheumatoid arthritis.

Positive skin reactions to extracts of hemolytic streptococci are present in a considerable percentage of rheumatic fever patients, and this has been stressed recently by Goldie,[26] who obtained positive reactions in 77 per cent of rheumatic fever cases and in only 32 per cent of controls.

It has been shown by numerous observers that rheumatic fever is particularly prone to follow hemolytic streptococcal infections of the throat or tonsils or accessory sinuses. Coburn and Pauli[18] found that agglutination and complement fixation reactions of sera from patients with rheumatic fever pointed definitely towards streptococcus infection. Furthermore they found that precipitin tests indicated that at the time of the rheumatic attack, patients develop in their blood specific precipitins to the protein fractions of the streptococcus hemolyticus. Finally, these same authors demonstrated that at the onset of rheumatic fever there occurs in each instance a rise in the antistreptolysin titer of the patient's serum. The authors consider this rise in antistreptolysin as particularly strong evidence of recent infection by the hemolytic streptococcus. These studies of Coburn have been repeatedly confirmed in various laboratories and certainly point strongly towards a streptococcal factor in the disease.

Virus Theory.—So-called virus bodies have been found in the exudates from various cases of rheumatic fever by Eagles,[20] Schlesinger[40] and others of the English school. These so-called elementary bodies are agglutinated by the patient's serum, but apparently possess no pathogenesis for animals. Until some definite proof of pathogenicity has been established, bacteriol-

ogists are not likely to give these studies very serious consideration. In our laboratory Dr. Angevine and Dr. Rothbard[4] have made repeated efforts to cultivate a virus from the blood and exudates of patients with rheumatic fever, but always without success.

With respect to the rôle of vitamin C deficiency in rheumatic fever, others have followed the original studies of Rinehart[37] and have thrown additional light on the subject. There seems to be some vitamin C deficiency in the blood of patients with rheumatic fever, but this has been found to be the case in almost any febrile infection, all of which militates against the theory that vitamin C deficiency plays an important part in the etiology of rheumatic fever.

It seems fitting at this point to say something further about the so-called pleuropneumonia-like organisms in their relation to rheumatic fever. Swift and Brown[45] have reported the finding of pleuropneumonia-like organisms in the joint fluids of cases of acute rheumatic fever. This was accomplished first by cultivation on the chorioallantoic membrane of chicks by frequent serial passages. After about five passages, characteristic lesions appeared which were not obtained with exudates from other sources and from which pleuropneumonia-like organisms were cultivated on suitable media. Secondly, by intranasal inoculation of mice with exudate or with suspensions of inoculated chorioallantoic membranes, they produced a pneumonia free from ordinary bacteria from which, directly or after filtration, they could produce the characteristic lesions on chorioallantoic membranes and could recover pleuropneumonia-like organisms by direct culture. In their article, however, they do not report the production of arthritis with these strains, and in a recent report by Swift[43] before the International Congress on Microbiology in New York City, he expressed serious doubt concerning the findings in his previous report.

In our investigations on rheumatism at Cornell, Angevine and Rothbard,[5] using the methods of Kleineberger,[34] have made repeated efforts to cultivate pleuropneumonia-like organisms from the blood, exudates, and pathological tissue of patients with rheumatic fever, but always without any success

Treatment of Rheumatic Fever.—There have been no outstanding new developments in treatment. Something, however, should be said about chemotherapy in relation to both rheumatic fever and rheumatoid arthritis. Swift, Moen and Hirst[46] have tried sulfanilamide in the treatment of chronic recurring rheumatic fever. No benefits were noted; indeed, the rheumatic manifestations were intensified. Disappointing results were also reported by Massell and Jones,[36] who treated 58 patients with rheumatic fever, including 7 with chorea. Quite negative results have been reported by other observers, and the drug is equally disappointing in the treatment of rheumatoid arthritis.

Of special interest, however, in the prevention of rheumatic fever are the recent studies of Coburn and Moore,[14] who have recently published an interesting study on the value of sulfanilamide in the prevention of rheumatic fever. Rheumatic children were given maintenance doses of the drug (about 2 Gm. daily) over a period of months and were observed with respect to the incidence of hemolytic streptococcus infections and recurrences of rheumatic fever. No toxic effects from the drug were observed. Only one of the twenty-six patients so treated contracted an infection with hemolytic streptococci in the throat flora, and only one of the twenty-six highly susceptible rheumatic children developed active rheumatism. However, sulfanilamide administered to rheumatic subjects after the onset of streptococcic throat infections did not prevent rheumatic recrudescences. This important contribution to the prophylaxis of rheumatic fever seems to offer real promise as a practical measure of preventing recurring attacks of the disease.

Experimental Arthritis.—Bacteriologists continue to be interested in the study of experimental arthritis. In our own laboratory the writer, in collaboration with Angevine and Rothbard,[9] have recently published the results of extensive study on experimental arthritis in rabbits produced with streptococci and other organisms. Experimental arthritis was produced successfully with both streptococcus hemolyticus and streptococcus viridans. However, we were also able to produce an arthritis with staphylococcus aureus, pneumococcus, and paratyphoid bacillus A. The pathological picture produced

by these bacteria was very similar to that produced by streptococci.

In the February number of the *Journal of Experimental Medicine* Angevine and Rothbard[8] have called attention to the mechanism by which bacteria become localized in the tissues of the joints and eyes. Histological examinations of sections from the eyes and joints of large numbers of rabbits injected with hemolytic streptococcic has clearly demonstrated that when arthritis or cyclitis occurs, the synovial villi and ciliary processes are the most frequent and usually the primary sites of inflammation. By special methods for demonstration of bacteria, it has been shown that bacteria which found lodgment in either an eye or a joint were demonstrable first in the vessels of ciliary processes or synovial villi. A localized synovitis or iridocyclitis is brought about by the localization of bacteria in the synovial villus and ciliary process. These experiments, which give a clearer insight into the pathogenesis of infectious arthritis and iritis, explain why both may occur in association with certain infectious diseases.

The streptococcal theory of arthritis and rheumatism still seems to me to be the favorite theory. Perhaps eventually, however, we may find that the joints are not actually infected, but become sensitized in some way which we do not yet quite understand. Faber[21] in 1915 sensitized the joints by intra-articular injections of killed green streptococci, and stated that subsequent intravenous injections of the same organism lodged more readily in the prepared joints. He regarded this sensitization as specific within set limits, although he did not claim that the sensitization was specific for various strains of streptococci. Swift and Boots[44] in 1923 sensitized the joints of rabbits by intra-articular injections of nonhemolytic streptococci and subsequently infected the animals with intravenous injections of streptococci. They concluded that, because arthritis developed in many nonsensitized as well as in sensitized joints, sensitization was not an important factor in the development of arthritis. More recently Dr. Angevine[6] has returned to this problem and has obtained some interesting results. Rabbits were injected either intravenously or intradermally with heat-killed hemolytic streptococci and subsequently injected intravenously with living organisms. Arthritis was produced in the intravenously immunized rabbits with a smaller number of bacteria than was required to produce the disease in normal or intradermally immunized animals.

In another series of experiments the right knee joints of rabbits received repeated injections of small amounts of either heat-killed streptococci or a nucleo-protein fraction. When the animals were subsequently infected intravenously with living cultures of the same organism, the previously injected joints were more susceptible to infection than were joints that had been injected either with heat-killed staphylococci or horse serum. In these studies, which have not as yet been published, it would appear that the relation of bacterial allergy to joint infection is a subject which has not yet been completely elucidated.

33 East 61st Street.

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CLINICAL ASPECTS OF VITAMIN B DEFICIENCIES*

NORMAN JOLLIFFE, M.D.
New York, N. Y.

THE vitamin B complex is known to contain at least a dozen fractions, four of which are available in crystalline form in amounts adequate for clinical use. These are thiamin chloride (B_1), riboflavin (B_2), nicotinic acid (p-p factor), and pyrodoxin (B_6). Another factor, pantothenic acid (filtrate factor), has recently been synthesized and is just now becoming available for clinical investigation. Through the controlled use of these crystalline B-vitamins, the clinical investigator has made progress hitherto impossible when only concentrates were available. This progress has been mainly in three directions:

1. In recognizing the particular clinical manifestations of deficiency of each of the crystalline B-vitamins.

2. In recognizing the true etiology of certain clinical syndromes.

3. In recognizing that deficiency diseases in man are usually not single but multiple.

The diagnosis of deficiency in the B-vitamins depends, at the present time, upon a clinical evaluation of the history and the signs and symptoms presented by the patient.[6] A vitamin B deficiency should be suspected in the following groups of persons:

1. *The Indigent and Low Income Groups.*—The average American diet affords a small margin of safety in the B-vitamins. In vitamin B_1 this margin amounts to only 20 to 80 per cent.[5] This safety margin, though below the optimum, provides sufficient amounts of the B-vitamins to protect against deficiency disease under ordinary physiologic conditions. As this diet is average, it follows that a considerable fraction of the American population must consume a superaverage and a considerable fraction a subaverage amount of the B-vitamins.

2. *Persons Who Have Erroneous Dietary Habits and Food Idiosyncrasies.*—Regular consumption of extra-dietary supplements of vitamin-free calories as obtained from sugar, corn syrup, alcohol, candy, pastries, or soft drinks, may render a marginal diet inadequate. In evaluating the adequacy of a diet we must always scrutinize the dietary of any subject who remem-

*From the Department of Medicine, New York University College of Medicine, and the Medical Service of the Psychiatric Division, Bellevue Hospital, New York. Read before the annual meeting of the Minnesota State Medical Association, Rochester, Minnesota, April 24, 1940.

bers what he has eaten. The average person consuming a mixed and varied dietary not limited by idiosyncrasies or restrictions rarely remembers this. The more varied the diet, the less likely it is to be inadequate.

3. *Alcohol Addicts.*—These subjects often consume amounts of vitamin-free alcohol sufficient to lower the vitamin calory ratios significantly, even when an otherwise adequate diet is maintained.[7,8,10] A smaller consumption of biologically good calories, and impaired absorption or utilization of the vitamin, are additional factors leading to vitamin deficiency in these subjects.

4. *Patients Having Diseases Altering the Vitamin B Requirements.*—The better known of these are listed in Table I. This table indicates the wide possibilities for the development of secondary vitamin deficiencies.

TABLE I. FACTORS ALTERING THE VITAMIN B_1 REQUIREMENT*

I. Increase in Total Metabolism
  A. Abnormal activity, as associated with
    1. Prolonged strenuous activity
    2. Delirium
    3. Manic depressive psychosis, manic type
  B. Fever, especially of long duration, as in
    1. Tuberculosis
    2. Typhoid
    3. Malaria
  C. Hyperthyroidism
  D. Pregnancy
  E. Rapid Growth
II. Faulty Assimilation
  A. Diarrhea, especially of long duration as in
    1. Ulcerative and mucous colitis
    2. Intestinal parasites
    3. Intestinal tuberculosis
    4. Sprue
  B. Gastrointestinal fistulæ
  C. Diseases of liver or gall bladder
  D. Achlorhydria
  E. Carcinoma of stomach
III. Increased Excretion
  A. Polyuria, as in
    1. Uncontrolled diabetes mellitus
    2. Diabetes insipidus
    3. Long continued excessive fluid intake, as in urinary tract infections
  B. Lactation

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Thiamin Deficiency

The signs and symptoms attributed to vitamin B_1 deficiency are legion, the most definite being anorexia, fatigue, a neurological and a circulatory syndrome. Anorexia and fatigue are nonspecific. In their presence the possibility of vitamin B_1 deficiency should be considered and confirmatory signs should be sought. When these symptoms occur without supporting objective signs, and do not definitely respond to thiamin therapy within seventy-two hours, they are probably not due to vitamin B_1 deficiency alone.[14]

The neurological manifestations of vitamin B_1 deficiency are those of bilateral and symmetrical polyneuritis involving first and predominantly the lower extremities. Peripheral neuritis that involves a single nerve, or that is not bilateral and symmetrical, or that does not involve first and predominantly the lower extremities is, in our experience, probably not due to vitamin B_1 deficiency alone. For such neuritides other etiological agents should be sought.

For the purpose of clinical investigation we have classified the neurological manifestations according to severity into four groups: suggestive, mild, moderate, and severe. Heaviness of the lower extremities, and calf muscle cramps are usually the first symptoms. These are followed by paresthesias in the toes and fingers, burning of the feet, and pains in the legs. It should be emphasized that pain, though nearly always present, can often be elicited only by a leading question. Calf muscle tenderness and plantar hyperesthesia are as a rule the earliest objective signs. The hyperesthesia may extend up the ankles and legs in a sock distribution. Vibratory sensation may be lost in the toes. These signs we classify as suggestive, and a positive diagnosis of polyneuritis is not made, as circulatory disturbances may cause these or very similar findings. When, however, in addition to these signs, the ankle jerks are absent, a diagnosis of mild polyneuritis can be made. As the deficiency continues, the sensory and motor changes advance, the knee jerks disappear, position sense in the toes becomes impaired, calf muscle atrophy develops, and foot drop follows. We classify this degree of involvement as moderate, provided the signs are confined to the lower extremities. When there is also involvement of the upper extremities, the spinal cord, or the cranial nerves, or when a "central neuritis" is present, we classify the polyneuritis as severe.

The circulatory manifestations of vitamin B_1 deficiency do not form a rigid clinical picture.[4,9,11] They may occur in a person whose circulatory system is otherwise normal, or they may be superimposed on one previously damaged by degen-

erative, hypertensive, or inflammatory disease. These circulatory manifestations, as observed by Weiss and Wilkins,[23,24] Jones and Sure[15] and in our clinic, may be classified as follows:

1. Edema and serous effusions occurring in the absence of congestive heart failure, enlarged heart, or recognized etiologic factors producing edema and serous effusions.

2. Edema and serous effusions occurring with supporting signs and symptoms of congestive heart failure, usually with definite roentgenographic evidence of cardiac enlargement.

3. Sudden circulatory collapse which may be the first manifestation of circulatory failure or may occur after other signs of circulatory failure are well advanced.

The circulatory manifestations of vitamin B_1 deficiency occur in about one-third of vitamin B_1 deficient subjects manifesting definite polyneuritis. They are more likely to occur in patients with suggestive or mild involvement than in those having advanced neuritis. This factor is related to the ability of persons with mild neuritis to perform muscular exertion.

Some of the more characteristic diagnostic features of the circulatory manifestations of vitamin B_1 deficiency are:

1. Mild nature of the polyneuritis.

2. Increased or normal velocity of the blood flow in the presence of congestive heart failure.

3. Rapid response to specific therapy with complete and permanent reversibility of the circulatory manifestations.

Riboflavin Deficiency

Riboflavin is a necessary constituent in the diet of many animals. In the rat its lack leads to failure in growth, to a senility, alopecia, a non-specific dermatitis and keratitis; in the dog an acute deficiency leads to spasticity, generalized weakness, circulatory collapse and a "yellow" liver, while a chronic partial deficiency results in signs characterized clinically by ataxia. Although riboflavin is presumably present in every living cell and is concerned with the chemical reactions involved in cell respiration, no distinct clinical syndrome in man had been attributed to its deficiency prior to Sebrell and Butler's[19] report.

The lesions produced by Sebrell and Butler in ten of eighteen women maintained on the diet of Goldberger and Tanner appeared ninety-four to 130 days after the beginning of the experiment. They began "as a pallor of the mucosa of the lip in the angles of the mouth without involvement of the buccal mucosa. This pallor was soon followed by maceration, and within a few days superficial transverse fissures appeared, usually bilateral, and exactly in the angle of the mouth. These fissures extended somewhat downward from the angle. . . . In some instances the fissures continued to extend onto the skin for a distance of as much as half an inch. These lesions resemble those described as perlèche. At about the time the fissures were seen, the lips became abnormally red along the line of closure. This was due apparently to a superficial denudation of the mucosa. In addition to the cheilosis, there was also seen a fine, scaly, slightly greasy desquamation on a mildly erythematous base in the nasolabial folds, on the alæ nasi, in the vestibule of the nose and on the ears."

Under the conditions of the experiment these lesions were alleviated by the administration of synthetic riboflavin, but not by nicotinic acid. The authors' conclusion that the condition is a manifestation of riboflavin deficiency seems warranted. Since then, Oden, Oden and Sebrell[18] have reported three patients from rural Georgia with similar lesions which responded promptly to 5 mg. of synthetic riboflavin given daily. They believe, since the Odens have seen many similar cases in their practice in rural Georgia, that ariboflavinosis is in all probability a common deficiency disease in the southern United States. Sydenstricker[22] thinks that these lesions are "even more frequent than frank pellagra." Sydenstricker's[16] group has reported, in addition, a keratitis associated with these signs of riboflavin deficiency in ten subjects.

We[13] have reported fifteen subjects having lesions due, we believe, to ariboflavinosis. Thirteen of these subjects were alcoholic, one had advanced pulmonary and intestinal tuberculosis and one was an epileptic. In this group of fifteen patients, thirteen had nicotinic acid deficiency, seven had vitamin B_1 deficiency and three had vitamin C deficiency. Only one patient had no clinical evidence of another vitamin deficiency. Since then, however, we have observed three additional subjects, all university students, who presented no clinical evidence of another deficiency disease. The facial lesions seen consisted of filiform

excrescences of a seborrheic nature, apparently derived from the sebaceous glands, varying in length up to 1 mm., closely to sparsely scattered over the skin of the face. Their characteristic location was in the nasolabial folds, but in addition they occurred frequently on the alæ nasi, occasionally on the bridge of the nose and sometimes on the forehead above the eyebrows. The skin on which the excrescenses were located was the seat of a fine, scaly, greasy desquamation. On casual inspection these filiform lesions resembled urea frost, but they could not be brushed off by rubbing with the fingers. In addition, most of the patients showed fissures and maceration at the angles of the mouth, and a degenerative crust-like formation on the epithelium of the lips, most marked on the lower. The fissures at the angles of the mouth were bilateral and extended laterally 1 to 3 mm. onto the mucous membrane of the mouth and 1 to 10 mm. onto the skin. They were usually very shallow but were sometimes 0.5 mm. deep, and their bases as a rule showed little or no increased redness. Extending for 5 to 20 mm. from the angle of the mouth onto both lips, the mucous membrane was macerated and wrinkled and pearl-gray. The lips, particularly the lower, frequently showed a marked increase in the vertical fissuring, often without a break in the mucous membrane. Occasionally, the vestibule of the nose was involved, with lesions similar to those on the lips. We observed no lesions on the ears.

Our first ten subjects, all of whom were pellagrins, were maintained with the diet of Goldberger and Tanner. After a control period of three to fifteen days, during which neither the facial lesions nor the cheilosis improved, various preparations then being tested for their value in the treatment of pellagra were given. Preparations which produced a cure of the stomatitis of pellagra were followed also by disappearance of the facial and lip lesions now ascribed to riboflavin deficiency. These were vegex, brewers' yeast and liver residue. Highly concentrated liver extract effective in pernicious anemia, as well as cod-liver oil, linseed oil, cevitamic acid and thiamin chloride were ineffective not only in pellagrous stomatitis but also on these facial and lip lesions. For this reason we believed that the lesions were all part of pellagra.

When, however, we began the treatment of our pellagrins with nicotinic acid while still maintaining them on the diet poor in the vitamin B complex, although we obtained dramatic responses in the oral, gastrointestinal and mental manifestations of pellagra, the facial and lip lesions were not affected. After the response to nicotinic acid, two of these patients were given a full diet supplemented with 18 gm. of vegex daily by mouth. The characteristic facial and lip lesions promptly improved.

At this time Sebrell and Butler's report appeared. Their description of the lesions which they had produced experimentally suggested to us that the lesions we had been observing in our subjects were probably signs of more advanced states of riboflavin deficiency. If true, this observation would explain their failure to respond to nicotinic acid and their response to a full diet plus vegex, brewers' yeast or liver residue, substances rich in riboflavin. We, therefore, determined to test the effect of synthetic riboflavin on the lesions occurring in our subjects.

By maintaining patients having these characteristic lesions of riboflavin deficiency with a diet poor in the B complex we demonstrated that these lesions respond to synthetic riboflavin, but not to thiamin chloride, nicotinic acid or vitamin B_6.

Nicotinic Acid Deficiencies

The signs and symptoms of partial chronic nicotinic acid deficiency, particularly those occurring in pellagrins, are so well known from the work of Spies, Sydenstricker and Smith and their co-workers that it is not necessary to describe them in detail. The complete picture consisting of a scarlet-red stomatitis and glossitis, diarrhea, bilateral symmetrical dermatitis and mental aberrations form in combination such a characteristic syndrome that they are widely recognized and should never go unrecognized. It is not so well understood, however, that the oral lesions, the gastro-intestinal lesions, the mental changes or the skin lesions may each occur alone or in any possible combination. For example, the patients having the stomatitis of nicotinic acid deficiency are too frequently considered to have only the superimposed Vincent's infection. The primary diagnosis is not considered and specific therapy is neglected. If nicotinic acid therapy is instituted not only is the scarlet-red stomatitis blanched within 24 to 48 hours, but the Vincent's infection heals without

other general or local therapy. The mental changes may precede the skin, gastrointestinal or oral changes and the patient may be labeled as a neurasthenic, neurotic or psychoneurotic. Similarly, gastrointestinal manifestations may precede all the others, and the diagnosis may be missed for many weeks.

We[12] have reported 150 cases of an "encephalopathic syndrome," a condition heretofore almost always fatal, which we believe is caused by nicotinic acid deficiency. This syndrome may occur as the only clinical manifestation of a deficiency disease or it may occur in association with pellagra, polyneuritis due to vitamin B_1 deficiency, the oculomotor disturbances of a "central neuritis," or scurvy. The clinical picture of this encephalopathic syndrome is more or less well defined and is characterized by clouding of consciousness, cogwheel rigidities of the extremities, and uncontrollable grasping and sucking reflexes.

Bender and Schilder,[2] who have described its clinical picture, included this syndrome as one of a group of five which they called collectively "encephalopathia alcoholica." Their classification of the types of encephalopathia alcoholica was related to the most prominent manifestations: (1) clouding of consciousness and changing rigidities, (2) cerebellar symptoms, (3) catatonia, (4) alcoholic delirium, and (5) polyneuritis. Groups 1 and 5 were clinically similar, the difference being that in group 1 the polyneuritis was minimal or absent while in group 5 the polyneuritis was so marked as to constitute the most prominent manifestation. We believe that these two groups are identical, differing only in the degree of clinical vitamin B_1 deficiency superimposed on a nicotinic acid deficiency or vice versa. Groups 2, 3 and 4 present different clinical pictures distinct from the specific encephalopathic syndrome reported herein. We also believe that the oculomotor disturbances when they occur are a manifestation of a disease process distinct from this specific encephalopathic syndrome. Likewise to be excluded are the encephalopathic manifestations of groping, grasping and sucking which may occur during the course of delirium tremens, acute alcoholic hallucinosis, expanding intracranial lesions, infectious diseases with delirium, advanced cerebral arteriosclerosis and other diseases.

The encephalopathic syndrome does not occur exclusively in alcoholic patients. Both Spies[20] and Sydenstricker[22] have observed this syndrome in endemic pellagrins. Some of the cases of pellagra described by Matthews[17] (cases 2 and 9) may very well have manifested this encephalopathic syndrome, although his report does not include recorded observations of grasping and sucking reflexes or of cogwheel rigidities of the extremities. Cleckley, Sydenstricker and Geeslin[3] have studied a group of subjects having stupor which responded to nicotinic acid therapy. We believe that several of their protocols are probably descriptions of the encephalopathic syndrome which we are reporting here. Prior to 1933, patients admitted to our service having this encephalopathic syndrome almost invariably died irrespective of the treatment given. Since most of the patients were dehydrated, it seemed reasonable to attempt hydration by infusions of 5 per cent dextrose in physiologic solution of sodium chloride. A total of forty-seven patients were thus treated (Table II), forty-five of whom died while exhibiting the encephalopathic syndrome. Three of these patients had other diseases which were probably fatal (pneumococcic penumonia, ruptured duodenal ulcer, subarachnoid hemorrhage); if these are discarded a corrected mortality of 89.4 per cent is obtained.

TABLE II. RELATION OF THERAPY ON 150 SUBJECTS HAVING THE ENCEPHALOPATHIC SYNDROME*

Treatment	Cases	Deaths No.	Deaths Percent	Died From Other Causes	Corrected Mortality Percent
House diet, dextrose and saline solution	47	45	95.7	3	89.4
House diet, dextrose and saline solution, thiamin chloride	15	15	100.0	0	100.0
Vitamin rich diet, dextrose and saline solution, vitamin B complex	66	41	62.2	7	51.5
Basal diet, dextrose and saline solution, nicotinic acid	22	7	31.8	4	13.6

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Most of these subjects had polyneuritis due to vitamin B_1 deficiency. A considerable number had stomatitis, which in fifteen instances is now recognized as having been similar to the stomatitis of patients with pellagra. Its frequent association with known deficiency diseases suggested that the encephalopathic syndrome too might be a manifestation of some nutritional lack. If so, then from its commonest associations the defi-

ciency would most likely be of one or more fractions of the vitamin B complex. That the encephalopathic syndrome also occurred independently, in the absence of other clinical evidence of deficiency disease, suggested the possible lack of a distinct and perhaps as yet unidentified nutritional element. Since polyneuritis was the commonest associated disease, we studied the effect of parenteral administration of from 50 to 200 mg. of thiamin chloride daily while continuing the routine treatment of hydration. The fifteen consecutive patients thus treated all died without improvement in the encephalopathic syndrome. The next group of these patients was treated with vitamin rich diets supplemented by oral and parenteral administration of large amounts of preparations rich in the B vitamins: vegex, brewers' yeast, an aqueous whole liver extract and various fractions of liver. Of the total of sixty-six patients thus treated, thirty-three had other signs now recognized as due to deficiency of nicotinic acid. Twenty-five, or 37.8 per cent of these patients recovered; the rest died while manifesting the encephalopathic syndrome, a mortality of 62.2 per cent. Seven patients in this group, however, had in addition a probably fatal disease (three advanced pulmonary tuberculosis, two pneumococcic pneumonia, one streptococcus hemolyticus sepsis, one cirrhosis of the liver); discarding these, we obtain a corrected mortality of 51.5 per cent. This experience supported our hypothesis that the responsible factor or factors must be sought in the vitamin B complex, excluding thiamin chloride.

Shortly after nicotinic acid became available, we began to test the effect of nicotinic acid on our patients having the encephalopathic syndrome. Twenty-two consecutive patients with the encephalopathic syndrome were treated with nicotinic acid, seven of whom died, giving a mortality of 31.8 per cent. This death rate should be compared with the mortality of 95.7 per cent in forty-seven subjects treated by hydration alone, the mortality of 100 per cent in fifteen subjects treated by hydration plus thiamin chloride and the mortality of 62.2 per cent in sixty-six subjects treated by hydration plus the entire vitamin B complex. In the three groups not given nicotinic acid each subject who died did so without prior recovery from the encephalopathic syndrome. In the group treated with nicotinic acid, four of the seven subjects who died did so one, two, four and ten days respectively after the disappearance of the encephalopathic syndrome and of diseases probably independently fatal (pneumococcic pneumonia, cirrhosis of the liver, streptococcus hemolyticus sepsis, multiple lung abscesses). On this basis the "corrected mortality" in the group treated with nicotinic acid is 13.6 per cent, as compared with 89.4, 100 and 51.5 per cent corrected mortality in the groups of patients not treated with nicotinic acid.

It seems unlikely that the response obtained for the patients treated with nicotinic acid could be due to some other factor. Hydration alone failed, hydration plus thiamin chloride failed, hydration plus vitamin B complex was partially effective but hydration plus nicotinic acid was successful in a large majority of cases. Assuming that nicotinic acid is the effective therapeutic agent, the significant decrease in mortality in the group treated with preparations containing the vitamin B complex can be attributed to the nicotinic acid content of those preparations. The failure of the same preparations in more than half of the treated subjects can be attributed to their relatively small content of nicotinic acid. That the results in the group treated with nicotinic acid were due to chance seems unlikely. Each group seems large enough for the results to be significant. It is noteworthy that before the use of nicotinic acid we had never witnessed recovery in four consecutive cases but had witnessed death in more than fifteen consecutive cases of the encephalopathic syndrome.

The fact that only about half of our subjects presented other signs of deficiency of nicotinic acid, and the fact that in endemic pellagra the encephalopathic syndrome occurs only in the more advanced and severe cases does not necessarily contravene the evidence that this encephalopathic syndrome is a manifestation of deficiency of nicotinic acid. Our explanation, which of course, is speculative, is as follows: As a complete deficiency of riboflavin leads to a different clinical picture than partial riboflavin deficiency, there may well be a similar difference in nicotinic acid deficiency. The encephalopathic syndrome represents, we believe, a complete nicotinic acid deficiency, while the pellagra syndrome (stomatitis, the gastro-intestinal, the common psychic symptoms and possibly the dermatitis) represents a partial deficiency of nicotinic acid not complete enough to produce the encephalo-

pathic syndrome. If this is so, patients having both pellagra and the encephalopathic syndrome would represent the picture of a partial deficiency of nicotinic acid of sufficient duration to cause the structural changes recognized as pellagra, on which has been superimposed a complete nicotinic acid deficiency, while patients showing the encephalopathic syndrome without signs of pellagra would represent a complete nicotinic acid deficiency which develops so rapidly that the structural changes in the mouth and skin characteristic of pellagra do not have time to occur.

Whether this explanation of the modus operandi is the correct one or not, it seems to us entirely justifiable on the basis of our observations, to attribute the etiology of the encephalopathic syndrome which we have described to nicotinic acid deficiency; as such, its proper label should be "nicotinic acid deficiency encephalopathy." By this designation we do not mean to imply that there are not other causes of encephalopathy, for disturbances in brain metabolism may and do occur as a result of other factors than lack of nicotinic acid. It is not to be expected that nicotinic acid should be effective in those cases or that its administration in appropriate instances will always result in cures, for the deficiency may be advanced to an irreversible stage.

Pyrodoxin

A specific syndrome in man attributable to a deficiency of vitamin B_6 or pyrodoxin has not as yet been reported. In rats, a deficiency of this vitamin is known to cause "rat acrodynia," foci of degeneration in striated and cardiac muscle and changes in the nervous system, particularly of the columns of the spinal cord. Antopol and Schotland[1] have recently suggested that vitamin B_6 through its pyridine structure may be involved in the enzyme system concerned in muscle metabolism. In this connection it is interesting to note that Spies[21] and his co-workers noted increased muscle strength in patients with pellagra following its administration; Antopol and Schotland have reported on its beneficial effect on muscle strength in six patients having pseudo-hypertrophic muscular dystrophy, but warned that "it is not to be implied that this group of muscular dystrophies are due to avitaminosis B_6." In addition we have accumulated evidence that vitamin B_6 plays some part in the acne syndrome.

Syndromes collectively labeled paralysis agitans, while not directly fatal, usually pursue a progressive course, and eventually the victims become helpless and seek hospitalization. Since muscular rigidity and weakness is characteristic of paralysis agitans, and since vitamin B_6 is involved in muscle metabolism, it seemed worthwhile to test its effect in this syndrome. We, therefore selected fifteen patients having paralysis agitans, all of whom were bedfast or chairfast, ten of these for more than three years. Six of our patients gave a history of encephalitis. All the patients received 50 or 100 mg. of vitamin B_6 hydrochloride by intravenous injection, either daily or every other day. Of the fifteen patients, four showed subjective and definite objective improvement. Two additional patients were subjectively improved. The following case histories are reported:

Case 1. A seventy-eight-year-old retired business man, was seen on November 15, 1939, because of aches and pains of ten days' duration, in all the extremities. Significant findings were stooped posture, expressionless face, and paucity of associated movements. An intention tremor of the hands was present. There were no rigidities. He was treated with diet, vitamin B-complex by mouth, liver extract and thiamin chloride parenterally. By January 2nd, the patient was worse, rising from a chair was a task, and rigidities of the extremities were now present. Thiamin chloride and liver extract were discontinued. Belladonna preparations were administered and continued at limit of tolerance until April 1. By March 1 the patient had to be helped in and out of bed, to dress, to shave and to bathe. He could rise from a chair only with difficulty but continued to feed himself. From that time he has been given 100 mg. of nicotinic acid three times daily. On March 23, as no improvement had been noted, he was given 100 mg. of vitamin B_6 by intravenous injection. This dosage has since then been repeated every other day. Within half an hour after the first dose, the patient could rise from a chair without difficulty, the rigidities became indiscernible, he could walk and he climbed stairs without assistance. By March 31, expression was again evident in the patient's face, and he was able to take short strolls outdoors. By April 6, he was able to bathe, shave and dress himself, and had gone to church. His posture is fairly erect. The associated movements have not returned and the intention tremor remains unaffected.

Case 2. A sixty-two-year-old white night watchman was admitted to Bellevue Hospital on March 13, 1940 because of helplessness of one week's duration and with a tremor of twenty years' duration. One week prior to admission, while at work, the patient fell and found himself helpless. Important findings were unintelligible speech, mask face, coarse tremors of the hands, and rigidities of all extremities. He was unable to rise in

bed or move his legs on command. He was given tincture of stramonium to point of tolerance. On March 25, his condition was unchanged and treatment with 100 mg. of vitamin B_6 daily by intravenous injection, plus 300 mg. of nicotinic acid and vitamin B-complex by mouth was begun. By April 8, the patient could feed himself, rise from a chair, and avail himself of toilet privileges. His face is mobile and his speech intelligible. The tremor is unimproved, the posture is bent, and the poverty of associated movements remains.

Case 3. A forty-seven-year-old laborer, was transferred to Bellevue Hospital on July 22, 1939, from the Farm Colony, where he had been a patient for two years. He was never ill until he had "influenza" in 1926 which lasted one week and was associated with drowsiness and double vision. Within three months the patient noticed tremor of the upper extremities. For seven years prior to admission to the Farm Colony he had been treated as an out patient at another hospital. Significant findings were expressionless face, unintelligible speech, half moon posture, paucity of associated movements, constant coarse tremors, and cogwheel rigidities of the upper extremities. He was treated with tincture of stramonium. During the following eight months the patient's condition remained unchanged. On March 25, he was transferred to this service, given vitamin B-complex plus nicotinic acid by mouth, and intravenous administration of 100 mg. daily of vitamin B_6 was started. During the first week no improvement was noticed. By April 8, there was subjectively an increase in strength, the tremor seemed diminished, and an increase in the emotional play of the face was commented on by all observers. The rigidities, posture, gait and poverty of associated movements seemed unchanged.

These cases represent examples of the so-called "arteriosclerotic," "idiopathic" and post-encepthalitic types of paralysis agitans. The first two are examples of degenerative diseases, the third of a sequel of an acute infection. The first two subjects represent in terms of function (as measured by ability to perform their normal occupation, disability of four months and four weeks respectively; the third nine years of disability. These factors may explain the prompt response of the first two subjects and the failure of the treatment in the third. The two patients whose histories are not detailed here, in whom definite objective improvement was noted, were both in the seventh decade. Neither gave a history of encephalitis, and both had disability for less than three years. Of the eleven patients who showed no objective improvement, ten had complete disability for more than three years, and half of these gave a history of encephalitis; the other had a disability of six months but gave a history of encephalitis. It is, therefore, emphasized that thus far objective beneficial results in helpless patients have been limited to lessening of rigidities and increase in strength in patients whose complete disability is of less than three years' duration, and who give no history of encephalitis.

In summary, the syndrome of paralysis agitans appears to include a group of persons whose manifestations, particularly the rigidities and weakness, respond to vitamin B_6.

Treatment of Vitamin B Deficiencies

In the treatment of deficiencies of the B vitamins I wish to stress two points:

1. Specific signs and symptoms of a specific deficiency responds promptly to adequate amounts of the specific chemical substance if the pathologic changes are not so advanced as to be irreversible.

2. Complete recovery of the patient does not always follow and adequate treatment does not consist of the administration of these specific chemicals either singly or in combination.

To illustrate these two points a case record is presented.

V. B., a thirty-four-year-old white female, was transferred to the Medical Service of the Psychiatric Division of Bellevue Hospital from an institution for the care of epileptics where she had been a patient for the past five years. When admitted she complained of weakness, bleeding gums, sore mouth and tongue, and a rash on the face and hands, all of some few weeks' duration. Her history included epileptic convulsions since the age of three, a craniotomy in 1932 without improvement in the convulsions, and an appendectomy in 1921. Her diet consisted chiefly of the following: Breakfast—oatmeal, coffee, and white bread; lunch—white bread and butter, potatoes, and a portion of stew; supper—tea, white bread and butter, prunes and apricots. She received one egg each week. The meat in the stew was never eaten by the patient, but given to others. In addition, she consumed daily large amounts of cake furnished by her parents so that the main constituents of her diet were cake and white bread.

Examination on admission showed a thin, undernourished, chronically ill female. She was coöperative, and oriented as to time, place and person. The epithelium of the lower lip showed degeneration with scaling and desquamation (cheilosis). There were fissures at the angles of the mouth extending about 2 mm. laterally in each direction from the mucocutaneous junction. There was moderate maceration of the tissues in the angles of the mouth. In the nasolabial folds and across the bridge of the nose there

was a seborrheic lesion consisting of filiform excrescences about 0.5 mm. in length, which appeared to protrude from the sebaceous glands. Superficially this lesion resembled urea frost, but it could not be rubbed off, and the underlying skin felt greasy. It was not present on the upper lip, vestibule of the nose, forehead or ears. In addition to this lesion there was an acneiform eruption over the face. The upper jaw was dentureless. The gums of the lower jaw were red and markedly piled up, consisting of bags of blood which bled on light touch. The tongue was clean, bald, and reddened as were the oral mucous membranes. Along the frenulum of the tongue were ulcerations covered by a pearl-gray exudate. On the right hand there was deep pigmentation over the second interphalangeal joint and thumb, a small ulceration over the knuckles, and a bracelet-like pigmented dermatitis of the wrist. The left hand exhibited a bracelet-like pigmented dermatitis and slight dermatitis over the second interphalangeal joint. There was increased keratosis of the elbows. There were no "necklace lesions" and no perineal lesions. There was no evidence of peripheral neuritis. A diagnosis of riboflavin, nicotinic acid and cevitamic acid deficiency, and epilepsy, was made.

The patient was maintained with the diet poor in vitamin B complex. Studies of the blood revealed total absence of cevitamic acid. The patient was then given 300 mg. of cevitamic acid daily by intravenous injection, and 100 mg. four times a day by mouth. On the second day of this regimen there was definite improvement and on the following day the gums were natural in color. The stomatitis and glossitis had remained unchanged. The dosage of cevitamic acid was then reduced to 200 mg. daily by mouth, and the diet poor in the vitamin B complex was continued. From the sixth day of hospitalization the patient was given 500 mg. of nicotinic acid daily, in doses of 100 mg. each, by mouth. By the eighth day of hospitalization the abnormal redness of the tongue and mucous membranes of the mouth had disappeared, the frenulum ulcer had healed, and the dermatitis of the hands was clearing. The lesions on the face and lips, however, were unchanged.

After eleven days of nicotinic acid therapy there seemed to be no significant change in the filiform lesions on the face or the lip lesions. Beginning on the seventeenth day of hospitalization administration of nicotinic acid was discontinued, but the patient was still maintained with the diet poor in the vitamin B complex; in addition, 10 mg. of synthetic riboflavin was administered daily by mouth. On the fifth day of this regimen a definite and marked improvement was noted. The degenerative epithelial lesions of the lips and the fissures at the angles of the mouth had cleared entirely, and the filiform lesions on the naso-labial folds and bridge of the nose had disappeared; the acneiform rash had also improved. The patient, however, now showed definite signs and symptoms of a mild peripheral neuritis characteristic of vitamin B_1 deficiency. She was then given 50 mg. of thiamin chloride daily by intramuscular injection. This was followed by complete disappearance of the signs and symptoms of peripheral neuritis within three days. At this time (the twenty-seventh day of hospitalization) the patient was given the house diet supplemented daily by 200 cc. of orange juice and 18 Gm. of vegex, and the administration of riboflavin, cevitamic acid and thiamin chloride were discontinued. The strength of the patient now markedly improved, and her weight increased from 84 pounds (on the twenty-seventh day of hospitalization) to 111 pounds when she was discharged on the fifty-third day of hospitalization.

These results demonstrate that the specific signs and symptoms of a deficiency disease respond to the appropriate pure chemical substances. By the use of these chemical substances the clinical investigator has learned that complete recovery of the patient does not always follow, and adequate treatment does not consist of the administration of these specific chemicals whether singly or in combination. This fact is amply demonstrated by this patient, for complete recovery, that is, gain in strength and weight, and disappearance of the acne, did not occur until a full diet supplemented by the entire vitamin B complex was administered. We believe, however, that a full diet plus the autolyzed brewers' yeast (vegex) furnishes other factors, both known and unknown, that cannot as yet be supplied by any known combination of pure chemical substances.

The vitamin B-complex preparations used in these studies were kindly furnished by The Vegex Co., New York; Lederle Laboratories, Pearl River, New York, and the Fleischman Laboratories, New York; the thiamin chloride, riboflavin, pyrodoxin and nicotinic acid by Merck and Co., Rahway, New Jersey.

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RECENT ADVANCES IN THE TREATMENT OF HEPATIC DISEASE*

ALBERT M. SNELL, M.D.

Rochester, Minnesota

IT has often been said that fundamental ideas of the nature of a disease determine to a greater extent than any other factor the manner of its treatment. If a condition is regarded as hopeless from the outset, an element of defeatism colors our therapeutic efforts. The various types of cirrhosis of the liver have been regarded for years as practically beyond the reach of treatment; they are, in fact, considered as affections which by their very nature "are above the powers of the constitution." [8]

Before considering some of the advances which are being made in the treatment of primary disease of the hepatic parenchyma, it is first necessary to establish the fact that hepatic lesions of this type are capable of making a response to therapy. One must survey the normal course of the disease to see what turn of events may be expected and what factors seem to influence prognosis. In this connection a study of experimentally produced hepatic disease brings out some interesting and important facts. Bollman and Mann were the first to show that only a very small part of the parenchyma of the liver is necessary to carry on normal metabolic functions, and that the body, therefore, contains hepatic tissue greatly in excess of the amount necessary to maintain normal activity. They have also been able to remove as much as 80 per cent of a dog's liver at one time without any particularly abnormal results. In addition to the anatomic and physiologic reserves possessed by the liver, an unusual degree of regenerative capacity is also apparent. When from a fifth to three-quarters of the liver has been removed from a dog, regeneration of a mass of hepatic tissue equal to or greater than the weight of the removed portion is completed in from six to eight weeks. Several factors, however, may be shown to diminish or to inhibit completely regeneration of the liver after removal of portions of its substance. Diversion of portal blood by the establishment of an Eck fistula, ligation of the common bile duct or the presence of preexisting damage to the parenchyma will exert such an effect.

If specific hepatotoxic substances, such as carbon tetrachloride, are given to the experimental animal, similar regenerative and reparative properties of the liver may be shown. By the use of repeated doses of such poisons, animals can be carried to a point that corresponds to the complete picture of atrophic portal cirrhosis in the human being. Even when this late stage of the disease is reached these animals can then be restored to normal health and a state of normal hepatic function. Naturally, one may ask whether under similar conditions, recoveries ever occur in the human being and whether the reserve and regenerative capacity of the liver of human beings ever reach the same extent. Because of the various stages at which the clinical disease is detected and because of differences in the type of treatment employed, it is difficult

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to find statistics on this point which are entirely satisfactory. In 1892, White reported that a review of the literature up to that time did not reveal a single case of uncomplicated cirrhosis of the liver with ascites which had long survived paracentesis; in his own series of cases, the time between the onset of symptoms and death averaged only about two months. In 1931, about forty years after White's report, Chapman, Rowntree and I reported a study of 112 cases of portal cirrhosis with ascites, encountered at The Mayo Clinic during the preceding six years. Eighty-four of these patients were treated according to a regimen that involved the use of a limited intake of fluid and salt and certain diuretic remedies. This plan of treatment, which was primarily directed at the removal of ascites and edema, was not without some beneficial effect. Of the 112 patients, eighty-four died and twenty-eight were alive at the time of the report. In the group in which survival did not occur, the average length of life after the development of ascites was sixteen months; of the twenty-eight patients living at the time of the report, the average length of life after the appearance of ascites was somewhat more than three years.

A more recent survey of the course of portal cirrhosis which is being carried out by Fleming at the clinic includes a study of the group of patients observed here from 1930 to 1937, inclusive. During this period, relatively less attention was paid to the matter of ascites and more to the maintenance of a high carbohydrate intake and to the improvement of the nutrition of the patient. There were 150 patients in Fleming's series of whom 128 are dead; the average duration of life after the appearance of ascites was about fourteen months, approximately the same as in the series studied by Chapman. Twenty-two of the patients in the more recently studied group are living, however, an average of almost six years after the first appearance of ascites. It is apparent from these two groups of figures that a not inconsiderable number of patients may survive even the more serious types of primary hepatic disease and that some ultimately regain a reasonably normal state of health. In both series of cases aforementioned, the greatest mortality appears to develop during the first six to twelve months after the appearance of ascites. Once this period has been passed the chances for survival, or even ultimate cure, appear to be considerably improved.

Because of the comparatively encouraging interpretation which may be placed on these two statistical reviews, we have attempted to initiate the same type of program for our patients who have clinical hepatic disease, a program which has been used successfully for experimental animals poisoned with carbon tetrachloride. This, in brief, consists of feeding an adequate diet of a composition which is regarded as optimal for the normal regeneration of hepatic tissue. For use in clinical subjects, vitamin supplements have been added to this regimen for reasons which will be considered in later paragraphs. The diet which has been used is high in carbohydrate, low in fat and rich in proteins not derived from meat sources. The food value is approximately 500 gm. of carbohydrate, 110 gm. of protein and about 60 gm. of fat with a total fuel value of about 3000 calories. The protein component of the diet has been derived chiefly from vegetables, milk and egg white, meat being kept at a minimum. The reason for this change in the protein composition was based entirely on experimental evidence. It has been shown by Bollman[2] that, although animals with experimentally produced hepatic injury are made worse by the administration of meat or meat extracts, the administration of protein from other sources is without harmful effect.

Our interest in the matter of vitamin supplements was stimulated primarily by the observations of Patek[13] who reported the effect of a high vitamin intake in a series of thirteen cases of alcoholic cirrhosis of the liver with ascites. Ten of these patients experienced remarkable improvement in respect to both clinical and laboratory findings; a few of the patients had spontaneous diuresis and the ascites disappeared. The vitamin supplements recommended by Patek, which we have used with various modifications, consisted of percomorphic acid (vitamins A and D), orange juice or pure ascorbic acid (vitamin C), Valentine's liver extract orally (as a source of riboflavin) or parenteral liver extract and yeast or a yeast concentrate plus thiamin chloride (to supply other portions of the B complex). In order to facilitate the absorption of the fat soluble vitamins, patients have been given 5 to 15 grains (0.3 to 1.0 gm.) of animal bile salts with meals.

Fleming has recently surveyed the results in a group of fifty cases in which this program was instituted during 1938 and 1939. The results are not entirely conclusive since hardly enough time has elapsed for the proper evaluation of this form of treatment. It appears, however, that about a half of the patients are living; about a third of the whole group are considerably improved and some appear to be making a complete recovery. This is a very satisfactory percentage of survival, especially since it includes patients treated during the critical first year after ascites developed. A few remarkable "cures" with disappearance of ascites have been encountered in this review, one of the most striking being in a man, aged seventy-two years, who after two years of almost weekly paracentesis has been free from ascites for one year and in good health. A number of patients have also made definite temporary improvement and later succumbed to hemorrhage from esophageal varices or from intercurrent infections. A review of the course of some of these cases indicates that the degree of improvement attained by the individual patient was to a great extent dependent on the regularity with which the program of therapy was followed.

These results and those previously reported by Patek are encouraging, especially because they concern a disease which has been regarded as virtually hopeless. It may be, of course, that coincidence and good luck have something to do with the matter. As Lennox has said of "cures" in cases of epilepsy, even the bloodiest of battles has thousands of survivors. The rationale of the therapeutic program has, however, something to recommend it. The dietary advised needs no defense, since all investigators of the clinical and experimental aspects of hepatic disease agree on its essential points. The use of vitamin supplements in large doses has recently been advised for almost all known ailments of human beings and their employment for hepatic disease may, of course, be referred to in the vernacular as "shot-gun" therapy or something worse. There is, however, a perfectly sound basis for this treatment in cases of hepatic disease which is not so widely known as it should be. The liver is a great storage depot for vitamins and perhaps for provitamins; its normally high content of vitamins A and D is well-known, as is the fact that it is one of the principal storehouses for vitamin C. It likewise stores the B complex or at least certain portions of it, and is essential in the utilization of vitamin K to form prothrombin. It is natural to suppose that in hepatic disease of advanced degree a state of deficiency in respect to one or more of these vitamins may develop.

Since it has been learned that the liver may be concerned in the metabolism of vitamins, a search has been made for vitamin deficiencies that develop in the course of hepatic disease, especially cirrhosis. It has been found that these states of deficiency are neither so rare nor so poorly defined as one might expect. For instance, vitamin A deficiency as characterized by absolute night blindness has been noted several times; an excellent study of the subject made by Patek[14] has shown that very large doses of vitamin A will gradually correct it whereas a diet that contains sufficient amounts of vitamin A to correct an ordinary deficiency state will not affect the condition. This observation implies that the ability of the cirrhotic liver to utilize vitamin A is definitely less than normal. Vitamin D deficiencies have also been demonstrated in hepatic disease chiefly as a form of osteoporosis; a few patients have been seen with advanced hepatic disease who show evidence of extensive loss of calcium from the bones. Disturbances of metabolism of another fat-soluble vitamin, the antihemorrhagic coagulation vitamin K, are well known and will be considered in a later paragraph. Defects in the utilization and storage of water-soluble vitamins are also apparent in certain cases. Deficiencies of vitamin C are rare; at least they seldom reach a degree sufficient to produce scurvy; but reductions in the concentration of ascorbic acid in the plasma and urine have been demonstrated. The relation of the B complex to cirrhosis requires consideration from a number of angles. It is, of course, a well-known fact that the patient with alcoholic cirrhosis has, ordinarily, subsisted on a diet deficient in the B complex. Recently, it has been shown by Rich and Hamilton that a diet adequate in respect to all its essential constituents and containing adequate amounts of thiamin chloride, nicotinic acid, riboflavin and vitamin B_6 was nevertheless capable of producing a marked cirrhosis in rabbits. Animals fed exactly the same diet but with yeast given instead of the various individual components of the B complex did not experience the development of hepatic lesions of any conse-

quence. In other words, a deficient intake of some unknown component of the B complex was capable of causing cirrhotic changes in the rabbit's liver. It is of interest to note in this connection that diets deficient in riboflavin will produce fatty metamorphosis of the liver in dogs, and that thiamin chloride (B_1) will maintain the liver glycogen of rabbits poisoned with carbon tetrachloride as well as favor normal regeneration (Hirata). When one examines the records of patients with hepatic cirrhosis for evidence of secondary B complex deficiencies, the typical clinical syndromes of peripheral neuritis, pellagra and cheilosis are found to be rare. Glossitis is occasionally noted but the oral lesions that one encounters in cases of pellagra are uncommon. Peripheral neuritis has also been observed; riboflavin deficiency (as characterized by cheilosis) has been observed by Jolliffe in the mouths of patients suffering from alcoholism and presumably from fatty changes in the liver. None of the usual clinical evidences of deficiency in vitamin B complex, however, are sufficiently marked to warrant attention for themselves alone and they are hardly numerous enough to indicate that ordinary types of avitaminosis-B play a significant part in the symptomatology of advanced hepatic disease.

There are, however, certain obscure and poorly understood features of portal cirrhosis which may have a bearing on the matter of deficiency of the vitamin B complex. It is now generally held that the liver has a very important rôle in the handling of thiamin. A few attempts have been made to determine whether or not normal storage of thiamin chloride obtains in persons who have cirrhosis; the results so far are not entirely conclusive but it does appear from the recent report of Robinson, Melnick and Field that patients with advanced hepatic injury have a low urinary output of thiamin and that they respond to a test dose of the material in a manner indicative of impairment of storage.

With pellagra, which represents a chronic form of deficiency of nicotinic acid, it is not uncommon for the urine to contain an abnormal concentration of porphyrin. There is a comparable large excretion of porphyrin after exposure to various hepatic and general poisons, notably alcohol.[4] Porphyrinuria is common in hepatic disease and during episodes of hepatic insufficiency the amounts of porphyrin in the urine may increase materially. This analogy with the state of affairs existing in the pellagrous subject suggests that a possible deficiency of nicotinic acid may enter into the production of certain symptoms of hepatic disease.

It should also be recalled that encephalopathic states have been seen associated with nutritional deficiencies which respond in a specific manner to the administration of nicotinic acid (Jolliffe). Various types of cerebral disturbances, of course, have been seen in both acute cases of pellagra and in acute cases of alcoholism. A somewhat similar type of disturbance of the central nervous system (coma hepaticum) may be seen in the course of hepatic cirrhosis; the condition is characterized by mental confusion progressing to deep stupor and muscular spasticity and evidences of cerebral irritation are associated features. At least three such patients in hepatic coma have been observed to respond in a striking manner to the continuous intravenous administration of glucose with large doses of thiamin chloride (100 to 150 mg.) and nicotinic acid (250 mg.). Whether such large doses are necessary is, of course, debatable but the results in the few cases studied have not been obtained from the therapy (glucose, oxygen) previously used. It may seem, at the moment, of little advantage to be able to revive a patient from hepatic coma and then be unable to prevent his death from some other form of hepatic insufficiency; however, patients have been known to survive one or more attacks of coma for long periods of time. One cannot, of course, draw conclusions from these isolated observations as to the effects of nicotinic acid and thiamin chloride but they are not entirely without significance.

There is one final reason to justify the use of the vitamin B complex and its various constituents for cirrhosis. Patients who have this disease derive an abnormally large proportion of calories from carbohydrate and therefore, presumably make unusual demands on the various enzyme systems which assist in the breakdown of glucose. Two of these enzymes (co-enzymes) which are active in the metabolism of glucose, are the phosphopyridine nucleotides, each of which contains a molecule of nicotinic acid. These are believed to be concerned with the metabolism of hexosephosphate. It has been established that this enzyme system is exhaustible; in fact, there is evidence to indicate that a high carbohydrate diet

will exaggerate a deficiency of nicotinic acid for this reason. Another stage of glucose metabolism which is affected by an analogous enzyme system is the breakdown of pyruvic acid. The coenzyme in this reaction (cocarboxylase) is the pyrophosphate of thiamin. It has long been known that thiamin depletion is easily attained and that the process may be hastened by a pure carbohydrate intake (at least in some experimental animals). Finally, riboflavin enters into the composition of the Warburg-Christian respiratory enzymes which are active in cellular oxidation reactions. Thus, there are three enzyme systems dependent for their functional activities on constituents of the B complex. If storage of these various fractions of the vitamin B complex is reduced by hepatic disease and if the diet used in the treatment of the disease makes unusual, if indirect, demands on these fractions, it is logical to attempt to supply them in increasing amounts. In actual practice our attempts to apply this principle, especially to the care of patients who have acute hepatic damage and patients who have evidence of hepatic insufficiency in the postoperative state, have been productive of some encouraging results.

The Control of Hemorrhage from Esophageal Varices

One of the most feared complications in the course of chronic hepatic disease is the rupture of an esophageal varix. This accident is one of the leading causes of mortality in cases of atrophic cirrhosis and is all too frequently responsible for the death of a patient who may otherwise be making good progress. No entirely satisfactory means of dealing with these varicosities, which because of their situation are peculiarly vulnerable, has yet been devised. Omentopexy may possibly serve to divert some of the blood from these channels and thus reduce the chances of rupture; direct ligation of the coronary veins of the gastrohepatic omentum and even splenectomy have a similar and more direct chance of accomplishing a similar reduction in blood flow. The risk of the performance of all these procedures and the technical difficulties of the last two have militated against their general use.

For some time, the suggestion has been made that direct injection of these varices through the esophagoscope be considered but, until recently, no successful procedure of this type has been reported. In 1939, Crafoord and Franckner of Stockholm reported the successful treatment of varices in this way and, more recently, H. J. Moersch has treated a patient in this manner. In the case which he described the varices were of such a size as to occlude almost completely the lumen of the gullet. After four injections of a 2.5 per cent solution of sodium morrhuate, the veins were greatly reduced in caliber and showed evidence of local thrombotic processes. The lumen of the esophagus had returned to almost normal caliber and the mucous membrane was distinctly less congested. It seems likely that treatment of this type may prove to be the most satisfactory method of controlling bleeding from the esophageal vessels.

The relationship between vitamin K and the hemorrhagic diathesis of hepatic disease is now well-known. The condition depends on a deficiency in prothrombin which in turn is not so much due to a lack of vitamin K as to a primary inability of the liver to form prothrombin even if adequate amounts of vitamin K are available. Prothrombin deficiencies have been produced experimentally by intoxication with chloroform and by partial hepatectomy. In the clinical field, analogous prothrombin deficiencies have been seen in cases of subacute and acute atrophy of the liver and in portal and biliary cirrhosis. Early attempts to manage such deficiencies in the same manner as had been found effective in cases of obstructive jaundice, that is, with vitamin K and bile salts, were found to be almost totally ineffective in some cases and only partially successful in others. This has also been the experience of other investigators.

With the introduction of the various naphthoquinone derivatives that exhibit vitamin K activity, it was hoped that this difficulty could be overcome and that, with the aid of these potent materials which could be administered parenterally, the prothrombin deficiency of primary hepatic disease could be corrected. This hope, however, has not been realized; even the use of the most active material employed to date (2-methyl-1, 4-naphthoquinone) has failed to control entirely the condition. This compound, and others of similar chemical composition, may, however, maintain the level of prothrombin at a point sufficiently high to prevent gross bleeding even in the presence of advanced hepatic injury.

The patient may thus be tided over a period of danger until time has been allowed for regeneration of hepatic cells. Bollman[1] has noted that a high carbohydrate intake enhances the protective effect of these quinone compounds to a considerable extent. The use of naphthoquinones along with every reasonable effort to expedite the process of liver regeneration may be expected to save a considerable number of patients from a fatal prothrombin deficiency. Failures are to be expected but at least partial control of the hemorrhagic state is now possible.

Summary

The experimental and clinical evidence cited indicate that the possibilities of survival or clinical cure in cases of primary chronic hepatic disease are not inconsiderable. One may suggest that the poor therapeutic results noted by earlier observers were due to the practice of limiting the diet, purging and administering diuretic remedies of various kinds. The scheme of treatment now advocated is based entirely on an attempt to secure optimal conditions of nutrition for the patient and to provide all vitamins in sufficient quantities to ensure adequate supplies for all enzymatic and cellular activities that are necessary to health. Until more is known of the specific requirements for the various "protective substances" in the presence of injury to the liver, such treatment will necessarily be on an empiric basis. The many studies on vitamin metabolism in respect to the liver which are being reported lead one to believe that there may be certain specific features of hepatic disease which will respond favorably to certain known components of vitamins. Much further study will be required to establish the soundness of the present plan of therapy; in the meantime it may be offered on the basis of its comparatively favorable record and because no other therapeutic attack offers as good a prospect for success.

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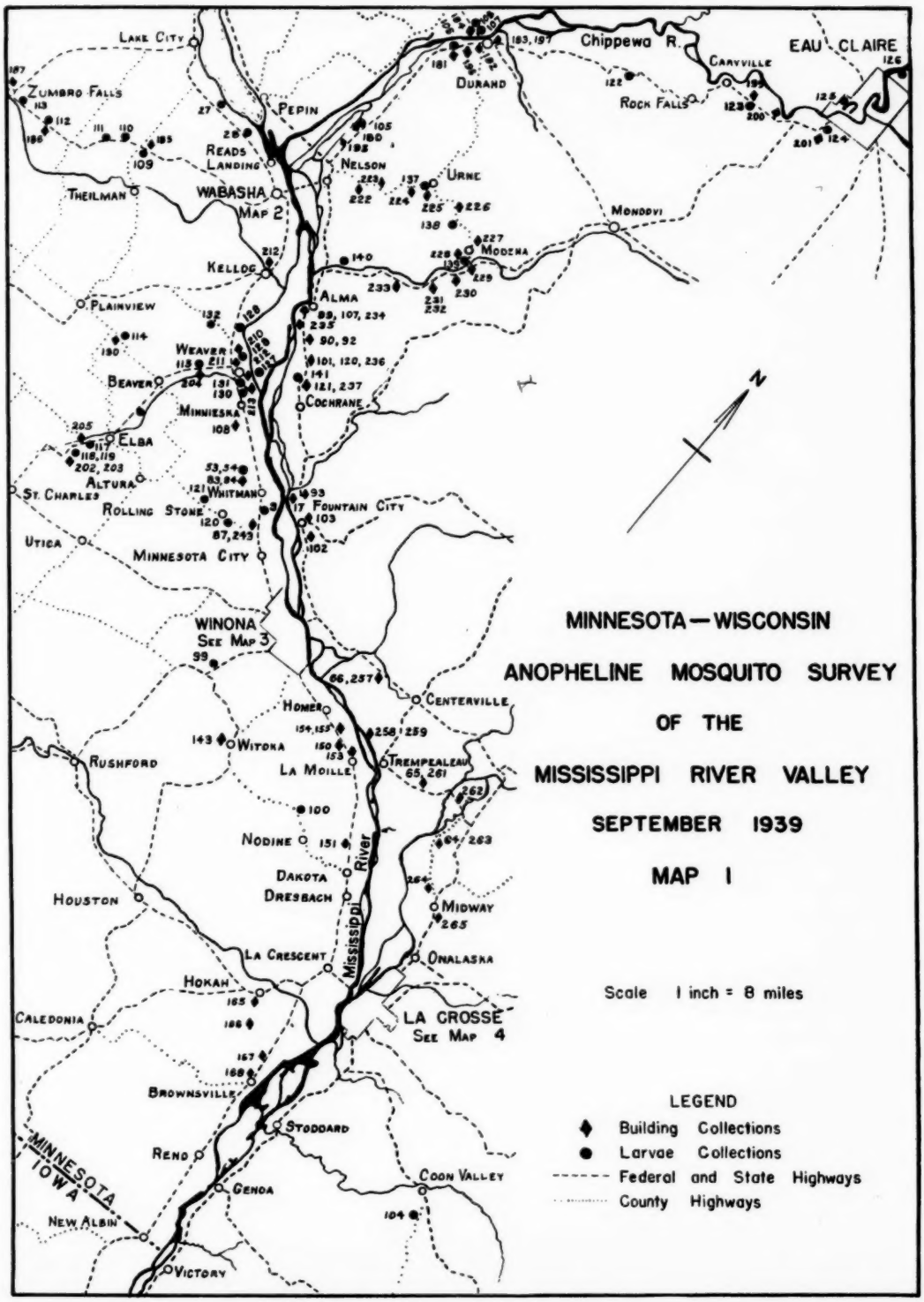
A PRELIMINARY SURVEY OF THE ANOPHELINE MOSQUITO FAUNA OF SOUTHEASTERN MINNESOTA AND ADJACENT WISCONSIN AREAS*

RICHARD H. DAGGY, OSWALD J. MUEGGE and WILLIAM A. RILEY
Saint Paul, Minnesota

DESPITE common belief that malaria does not occur in Minnesota and Wisconsin, it is well known to those in touch with the situation that locally acquired cases occasionally present themselves. There is current an impression that such cases are on the increase since the installation of the dams for improvement of navigation along the Mississippi River. The increasing number of cases of the disease reported to the Minnesota and Wisconsin State Health Departments would seem to afford some evidence in support of this view.

In Minnesota there were reported for the three seasons 1935-1937, inclusive, a total of nineteen cases, of which seven were clearly indigenous and two others presumably so. In 1938 there were eight reported cases, of which three were indigenous. In 1939 there were recorded twenty-

*This paper embodies partial results of a coöperative study made with the aid of the U. S. Public Health Service, by the Minnesota and Wisconsin State Health Departments, covering the period August 25 to September 26, 1939.


MINNESOTA—WISCONSIN
ANOPHELINE MOSQUITO SURVEY
OF THE
MISSISSIPPI RIVER VALLEY
SEPTEMBER 1939
MAP 1
Scale 1 inch = 8 miles
LEGEND
Building Collections
Larvae Collections
Federal and State Highways
County Highways
N
Lake City
Zumbro Falls
Pepin
Reads Landing
Nelson
Durand
Chippewa R.
Eau Claire
Carvville
Rock Falls
Theilman
Wabasha
Map 2
Urne
Mondovi
Kellog
Alma
Modena
Plainview
Weaver
Beaver
Cochrane
Minnieska
Elba
Altura
St. Charles
Whitman
Rolling Stone
Fountain City
Utica
Minnesota City
Winona
See Map 3
Homer
Centerville
Witoka
Rushford
La Moille
Trempealeau
Nodine
Dakota
Dresbach
Houston
Midway
La Crescent
Onalaska
Hokah
Caledonia
La Crosse
See Map 4
Brownsville
Stoddard
Reno
Genoa
Coon Valley
Minnesota
Iowa
New Albin
Victory
Mississippi River

two cases. Parallel conditions prevailed in Wisconsin where there was reported for the three seasons 1935-1937 a total of twenty cases, of which twelve were indigenous. In 1938 there were seven reported, of which five, occurring in cities bordering the Mississippi River, were indigenous. In 1939 the number of reported cases reached twenty-eight.

Associated in the work were Harold Peters, H. Laurence Burdick and Robert Dicke, without whose efficient aid the scope of the work would have been greatly restricted. Acknowledgements are also due Mr. Theodore Olson, Biologist of the Minnesota State Department of Health, who kept in close touch with the studies and who, as did Mr. Peters, made numerous photographs illustrating typical breeding places.

Four species of anophelines, each a potential malaria carrier, occur in Minnesota. These are *Anopheles maculipennis, A. punctipennis, A. quadrimaculatus,* and *A. walkeri.* Data regarding their incidence and distribution are few, as compared with those relating to other insects of economic importance. In view of the awakened interest in malaria, Dr. A. J. Chesley, Secretary and Executive Officer of the Minnesota State Board of Health, in August, 1939, suggested to Dr. C. A. Harper, State Health Officer of Wisconsin, that an intensive survey be made of the anopheline fauna along the Mississippi River, on both sides, from Wabasha, Minnesota, to La Crosse, Wisconsin. Late as the season was, it was evident that important data relative to the incidence and breeding habits of the various species might still be obtained.

The project and the necessary expenditures of federal funds were promptly approved and equipment assembled. On August 26 a general survey of the area under consideration (see map) was made to determine the most favorable location for the field laboratory. Ready access to a bridge, to boats, and to typical flooded areas on both sides of the Mississippi led to the selection of Wabasha, Minnesota, as headquarters for both the Minnesota and the Wisconsin field workers. A cabin adjacent to a considerable swampy area was available and intensive work was begun on August 27.

Methods of Work

In so far as the limited time permitted, four main lines of work, as follows, were carried out:

1. *Building collections* were made over as many scattered localities in the area as was feasible. Regardless of species, mosquitoes resting in sheds, outdoor privies, bath houses, basements, and similar shelters, were collected by the use of an aspirator. Search was also made beneath bridges and culverts. The total collections were counted and the anophelines identified.

2. Collection of anophelines attacking the workers was carried out to only a limited degree.

3. *Light trap catches,* utilizing the available two and, for a part of the time, three of the well-known New Jersey electrically controlled mosquito traps, were made during the entire period of the survey.

4. *Larval collections* were particularly emphasized, with a view to determining the extent of favorable breeding places. To insure correct identifications the specimens were usually bred out.

The survey was most fortunate in securing, through the courtesy of the District Engineer, U. S. War Department, a set of the maps prepared in connection with the river improvement project. These consisted of key maps to the various regions in the valley as well as a number of detailed maps showing areas of marsh, open water, flood plain forest, streams, et cetera, on a large scale. Although various changes have occurred in the course of completion of the dams, the maps were invaluable aids for the field studies.

Records of temperature and other weather conditions were kept throughout the work. These and other details will be filed for future reference and additions.

September weather in Minnesota is very undependable and the group was fortunate in having a full month, August 27 to September 27, of practically uninterrupted field work. According to the Weather Bureau monthly summary the mean temperature for September was 69.1° F., a departure of +6.6°.

Collections from Buildings and Other Shelters

In the course of the work, mosquitoes were taken from many kinds of diurnal resting places. These included privies, basements, sheds, bath houses, bridges, culverts, cattle underpasses and other shelters. All resting mosquitoes, including the non-anophelines, were collected from as many different localities in the area, as time per-

mitted. Of the 12,321 specimens thus secured, 11,798, or 95.7 per cent, were anophelines.

As illustrative of the conditions in buildings, exclusive of other shelters, we may consider the results at Wabasha, where collections were made daily in the basement of the field laboratory and in each of three outdoor privies near the laboratory.

For the period August 27 to September 26, 1939, there were 4,853 mosquitoes collected from these four stations. Of the total, only 79, or 1.6 per cent, were non-anophelines.

There were 4,774 anophelines, or 98.4 per cent, of the total catch. These were distributed as follows:

Anopheles quadrimaculatus	4,500	94.4%
A. punctipennis	262	5.4%
A. walkeri	12	0.2%
A. maculipennis	..	..

The enormous preponderance of *A. quadrimaculatus* in building collections was clearly indicated from the outset but was quite at variance with such distribution records as were available in the entomological collections of the University of Minnesota. Such records indicated a probable greater incidence of *A. punctipennis* in southeastern Minnesota. As we shall see, this was due to the fact that most of the previous collections had been made at points not on the Mississippi.

Examination of the detailed report of collections shows that there was a daily influx of anophelines and particularly of *quadrimaculatus* into these buildings. Even though removed daily, large numbers were always present the following morning. Thus, on the morning of September 3, 243 specimens were captured in the basement, although it had been cleared carefully the day before. On September 16, 231 specimens of *quadrimaculatus* were collected from one of the privies.

The picture is essentially the same when the total collections of 11,191 mosquitoes from buildings and other resting places throughout the river valley area are considered. The anophelines constituted 95.9 per cent of the catch and of these *quadrimaculatus* represented 91.7 per cent.

A significant contrast is afforded by the collections made in the surrounding hills and valleys, outside of the river valley proper. In these localities, referred to in subsequent discussion as "inland," there were taken 1,130 adult specimens from resting places comparable to those searched in the river valley. Again the anophelines were dominant, being represented by 1,070 specimens, or 94.7 per cent. The distribution of species was strikingly different from that found in the river valley. *Punctipennis* led with 917 specimens, or 85.7 per cent, while *quadrimaculatus* was represented by only 151, or 14.1 per cent, as compared with the total of 94.7 per cent found in the river valley collections from similar shelters. *A. walkeri* and *A. maculipennis* were represented by a single specimen each.

These findings agree with previous records indicating that *punctipennis* is the most common widely distributed anopheline in southern Minnesota. It breeds by preference in spring-fed streams and pools among the hills of this region, a fact which is in agreement with the known habits of the species.

While there is ample evidence to support the view that *quadrimaculatus* is the chief carrier of malaria in the southern United States, there should be further investigation before it is concluded that it plays an equally important rôle in Minnesota. As bearing on this question it should be noted that most of the dwelling houses in the area are well screened and that *walkeri*, also an efficient carrier, readily attacks man in the open, even in mid-day, in bright sunlight.

Anophelines Caught While Attacking

Throughout the survey specimens of anophelines feeding on man in the open were collected. Unfortunately time did not permit extensive collecting of this type and the following data represent occasional catches during the course of other work. On three occasions a definite attempt was made to obtain feeding records.

Of the total catch of 134 mosquitoes *quadrimaculatus* supplied sixteen, or 11.9 per cent. *A. walkeri* was represented by 114, or 85.1 per cent, *punctipennis* by four, or 3 per cent, and no specimens of *maculipennis* were so taken.

Of the 114 *walkeri*, fifty-five were collected when a definite effort was made to obtain feeding records. These collections were made on three successive days.

Obviously the data on feeding habits are so meager as to be merely suggestive. However, the preponderance of *walkeri* was also noted in similar catches of feeding mosquitoes made by William Chalgren, in 1938, in the Minneapolis-St. Paul area. Of 4,166 specimens, representing

TABLE I. SUMMARY OF LIGHT TRAP CATCHES AT WABASHA, MINNESOTA

August 26-September 25, 1939

	LIGHT TRAP A		LIGHT TRAP C		LIGHT TRAPS A AND C	
Anopheles quadrimaculatus	632	18.2%	1,061	74.4%	1,693	34.5%
Anopheles punctipennis	493	14.1%	130	9.1%	623	12.7%
Anopheles walkeri	2,357	67.7%	234	16.4%	2,591	52.8%
Anopheles maculipennis	..	..	1	..	1	..
Total Anophelines	3,482	100.0%	1,426	100.0%	4,908	100.0%
Total Anophelines	3,482	22.0%	1,426	21.3%	4,908	28.1%
Total Non-Anophelines	12,322	78.0%	5,272	78.7%	17,594	71.9%
	15,804	100.0%	6,698	100.0%	22,502	100.0%

twenty-one species, *walkeri* was the only anopheline, and of it forty-seven specimens were taken. The relative frequency with which it occurred in trap catches also indicates that it may be more important than ordinarily has been considered.

Light Trap Catches

Three electrically controlled mosquito traps of the New Jersey type, which has become standard for mosquito survey work, were available and two of them were in use for the entire period, at Wabasha. The third was operated for a five-day period at La Crosse, Wisconsin.

Of those in use at Wabasha, trap "A" was suspended in an apple tree close to the laboratory, on a ridge overlooking an extensive mosquito-breeding swamp (Fig. 1). Trap "C" was located in a back yard in the residential district known as West Wabasha.

From trap "A" 15,804 mosquitoes were taken during the period August 26 to September 24 (Table I). Of these 3,482, or 22 per cent, were anophelines, the percentage in the daily catches ranging from four on August 29, to a high of 51.4 on September 18.

The total daily catch as well as the percentage of anophelines varied. On two occasions, no mosquitoes were collected. This occurred on September 23 and again on September 25, when the light trap studies were concluded because of cold weather.

The largest single catch occurred on the night of September 15 when 2,264 mosquitoes were collected. Of these, 740, or 30.6 per cent, were anophelines. This record catch was made at the hottest period of the survey, a situation noted by other workers using light traps in sampling mosquito populations in other regions. Examination of the humidity records did not show any definite effects due to variations in this factor.

When one considers the distribution of the species captured by trap "A," he is immediately struck by the preponderance of *walkeri,* which is generally referred to in literature as an uncommon species. In the course of the month during which this trap was operated, 2,357 specimens of *walkeri,* or 67.7 per cent of the total anophelines, were taken as contrasted with 632, or 18.2 per cent of *quadrimaculatus.* It is the more striking in view of the fact that the trap was hung in the location where such large collections of *quadrimaculatus* were made in buildings. That it was not due to failure of the traps to attract the latter is evident when it is noted that the condition was almost completely reversed with trap "C," where 74.4 per cent were *quadrimaculatus* and only 16.4 per cent were *walkeri.* When the catches of the two traps are combined it is seen that a little over half of the anophelines were *walkeri,* around one-third *quadrimaculatus* and an eighth *punctipennis.*

Trap "C," instead of hanging in the open, near the edge of an extensive breeding place, as was trap "A," was in a yard with crowded shrubbery, in a residential district. The total number of mosquitoes caught here during the season was 6,698 compared with 15,804 at "A." It is interesting to find that the percentages of anophelines were almost identical—22 for trap "A" and 21.3 for "C."

In the absence of more complete data it is difficult to explain these differences in the catches from the two traps, located only two miles apart. They were identical in construction and light bulbs of the same intensity were used. Breeding conditions for anophelines were more favorable in the surroundings of trap "A," but also existed more remotely within range of "C." That *quadrimaculatus* was present in abundance in the former locality is shown by the fact that 4,500 speci-

mens were collected from the basement and the three outbuildings routinely inspected. Unfortunately only meager indoor collections were made in the region of "C" and hence comparisons between the two areas in this respect are not possible.

The discrepancies in the performance of the two traps serve to emphasize a fact well-known to workers accustomed to their use—it is not safe to rely on one or two traps to give a true picture of the mosquito fauna of a region. Care must be taken to select different significant locations or carefully to select comparable areas if information concerning their relative breeding is sought.

While more extensive collections from buildings might have cleared up the discrepancies in the data relative to catches of *quadrimaculatus*, there remains the more puzzling question as to the reason for the great numbers of *walkeri* taken with trap "A" as compared with those from "C." Earlier studies had convinced us that the species is common in Minnesota and that it feeds readily in the open, at any time of day.

That *walkeri* is not a household mosquito is indicated by the fact that only twelve specimens were included in the routine collections from buildings at Wabasha. It seems probable that it does not penetrate into residential districts as readily as does *quadrimaculatus* or is more restricted in its flight from breeding places. However, the fact that *walkeri* may overwinter in the egg stage (Matheson and Hurlbut, 1937; Hurlbut, 1938) might account for its being less attracted to houses during the period covered by this survey.

Light trap collections in the Minneapolis-St. Paul area as well as our experience with trap "A" suggest that *walkeri* may more readily be attracted to lights than are the other anophelines in this region. Johnson (1936) found that from 15 to 50 per cent of the anophelines caught by a light trap at Reelfoot Lake, Tennessee, were of this species, although it was very scarce in collections from buildings and in the larval surveys.

It is evident that further studies of the biology, distribution, and incidence of *A. walkeri* are highly desirable, particularly since it is known to be capable of transmitting both *Plasmodium vivax* (experiments of Matheson, Boyd and Stratman-Thomas, 1933) and *Plasmodium falciparum* (experiments of Kitchen and Bradley, 1936). Recently Bang, Quinley and Simpson, 1940, reported finding a wild-caught specimen harboring malarial parasites. The salivary glands were heavily infected and six oöcysts were found on the stomach.

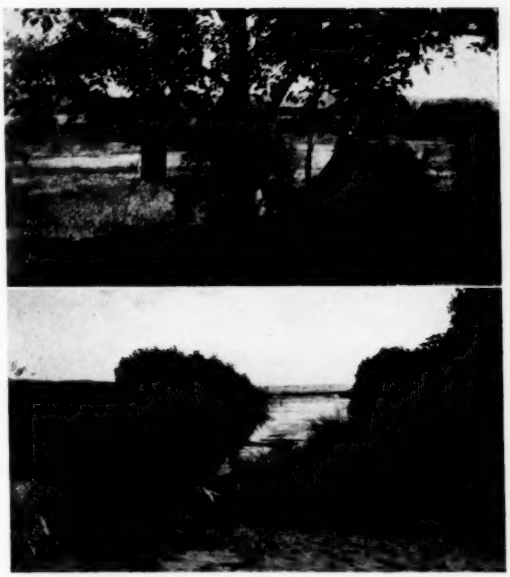


Fig. 1. (above) Trap "A" and a portion of the extensive swampy area below the laboratory at Wabasha, Minnesota. Photo by Harold Peters.

Fig. 2. (below) Backwater area with algal mats in which anophelines were breeding in numbers, near the field laboratory. Photo by Harold Peters.

The above-discussed light trap data relate to conditions at Wabasha, Minnesota, where the two traps were run throughout the entire period, August 26 to September 25. A third trap of the same type was operated at La Crosse, Wisconsin, for the five-day period September 12 to 16, during which larval surveys and building collections were being made in the vicinity. The trap was located on the edge of the main channel of the Mississippi river, on La Plume Island. A total of 1,751 mosquitoes was collected here—less than that of either of the Wabasha traps for the same period. Of this total, *walkeri* was by far the most abundant anopheline, constituting 84.7 per cent of the 483 taken, while *quadrimaculatus* made up 15.1 per cent. A single specimen of *punctipennis* was included in the catch.

For purposes of comparison the catches of the La Crosse and the two Wabasha traps for the same five-day period are given in Table II. Since the La Crosse trap was in a position somewhat similar to that of trap "A" at Wabasha, the

TABLE II. A COMPARISON OF THE LIGHT TRAP CATCHES AT LA CROSSE AND AT WABASHA FOR THE FIVE-DAY PERIOD SEPTEMBER 12-16, 1939

	LA CROSSE		LIGHT TRAP A (Wabasha)		LIGHT TRAP C (Wabasha)	
Anopheles quadrimaculatus	73	15.1%	290	16.6%	478	75.8%
Anopheles punctipennis	1	.2%	249	14.3%	43	6.8%
Anopheles walkeri	409	84.7%	1,206	69.1%	110	17.4%
Anopheles maculipennis	..	..	..	..	..	..
Total Anophelines	483	100.0%	1,745	100.0%	631	100.0%
Total Anophelines	483	27.6%	1,745	35.4%	631	26.6%
Total Non-Anophelines	1,268	72.4%	3,191	64.6%	1,740	73.4%
	1,751	100.0%	4,936	100.0%	2,371	100.0%

catches of the two might be expected to be very comparable. The percentages of *quadrimaculatus* were almost identical. *Punctipennis,* with its single representative, was practically lacking in the La Crosse catch, while *walkeri* was even more predominant than at Wabasha, Trap "A."

In view of this close agreement it is apparent that the anopheline populations at the two extremes of the surveyed area are very much alike. It is believed from these and supplementary studies that the entire valley between these points would yield similar results if the mosquito populations were similarly sampled.

Larval Survey

Most of the actual time for the month of the survey was spent in the field locating important anopheline breeding places. The surveys were more or less centered at Wabasha, Reads Landing, Winona, and La Crosse, which, as seen by the map, afforded typical conditions for the river valley. Some collections were made at additional points of interest and two days were devoted to inland surveys, away from the valley proper.

A total of 102 collections of anopheline larvæ were made in the river valley, the larvæ being taken to the laboratory and usually reared. No mosquitoes were reared from thirteen of the collections, in most of which the anophelines were not abundant and such as were present were in early instars. For the other eighty-nine collections, adults in numbers were recovered. Detailed records were kept as to the stations studied, the typical vegetation, the amount of shade or exposure, presence of fish and other significant data. These and the field notes are on file and will serve as a basis for more extended work in the future.

The anopheline larvæ were generally found in clean, quiet waters with abundant vegetation. Sloughs, sluggish streams, impounded waters behind wing dams and similar situations all through the surveyed area were favored breeding places. Dense tangled thickets of submerged *Ceratophyllum, Myriophyllum* and occasionally of *Potamogeton* with algal mats of *Spirogyra* and, more often, of *Hydrodictyon* (Fig. 2) were particularly favored by *quadrimaculatus* and *punctipennis.* Scattered over these areas there were often the duckweeds *Lemna* and *Wolffia,* but when they were present to the extent of thick, almost solid, layers, the larvæ were not present in numbers. As was to be expected, situations where vegetation was not abundant, and the water was deeper, and accessible to fish, yielded few anopheline larvæ.

All four species were obtained in these larval collections. Of a total of 948 reared, 544, or 57.4 per cent were *quadrimaculatus.* Second was *punctipennis* with a total of 366 reared adults, or 38.6 per cent. *Walkeri* was represented by only thirty-seven reared adults, or 3.9 per cent and *maculipennis* by a single one.

From these data, obviously very meager and based on restricted seasonal collecting, it would appear that *quadrimaculatus* and *punctipennis* are the most common two anophelines breeding in the sloughs and impounded waters in the valley. Of the eighty-nine larval collections, thirty-four yielded adults of both species, while twenty yielded only *punctipennis* and twenty-two *quadrimaculatus.* It should be pointed out that only one or two adults were reared from many of these latter samples.

How this condition compares with what existed before the installation of the dams cannot accurately be determined. The whole area was swampy and subject to overflow, affording many favorable breeding places for breeding of *quadrimaculatus* especially. However, much of the

swamp was covered by trees which were removed in the course of the river improvement program and this exposure to light rendered it more attractive to the anophelines. It is highly probable that there is greatly increased breeding by *quadrimaculatus* in the river valley.

Relative to *walkeri* there are a number of puzzling questions which can be answered only by further detailed studies. As we have seen, it was by a very wide margin the dominant species taken in light trap "A" and at La Crosse, both of which were located near marshy breeding areas and not in residential districts as was trap "C." It was also the species most frequently taken while attacking man. Why was it represented only to the extent of 3.9 per cent in the larval collections?

The most obvious answer to this question would appear to be that the particular breeding places favored by *walkeri* were overlooked in the larval survey. This may be the case although the larval survey was most intense in the Wabasha area and particularly in the area from which trap "A" attracted mosquitoes. It seems improbable that any important concentrated breeding area of *walkeri* would be overlooked, especially when all types were being examined here from the beginning of the survey. Another possibility is that the favorable breeding period for *walkeri* had passed before the survey began. Of this we have no evidence, beyond indications, that the species overwinters in the egg stage in the North, in which case the summer broods would have already completed their development and no larvæ would be hatching.

Such limited data as are at present available suggest that *walkeri* favors flooded grassy areas in shallow water for breeding. These areas were on some occasions cut grass, but probably included sedges and rushes as well. In most cases these stations were rated as poor because larvæ were not abundant. However, these grassy areas do cover large extents of bottom land and even though *walkeri* larvæ are sparsely scattered over them, the total emergence might be very great.

If this proves to be the breeding habit of *walkeri*, it affords one explanation of the species being obtained so infrequently in the larval survey. With the time strictly limited, the area to be examined very extensive, and the possibility of weather conditions limiting the survey, each collecting stop was brief and if no larvæ, or a very few, were found, the collectors moved on to another station. This resulted in emphasis on areas where larvæ were concentrated. Thus, if *walkeri* does not breed in concentrated areas as do *quadrimaculatus* and *punctipennis*, it would very likely be missed.

This may also account for difficulties others have experienced in locating the breeding places of the species. Bradley and McNeel (1935) in Florida and Johnson (1936) in Tennessee, found *walkeri* readily attracted to light traps but also had great difficulty in locating breeding places. Johnson reared only one adult from all nearby breeding places, while Bradley collected only eight larvæ.

In order to learn how extensively the four species of anophelines occurred elsewhere in the general region, two days were spent in a survey away from the river valley. The topography of these areas of southeastern Minnesota and corresponding sections of Wisconsin is rough and hilly. Much of it is unglaciated and hence drainage is well developed, with no ponds, lakes, or marshes to serve as mosquito breeding places. The only favorable places are springs, spring pools, seepage pools and small clear streams. In all of these locations larvæ were found in numbers.

By far the dominant species in the whole range of differing habitats was *A. punctipennis*, which constituted 98.8 per cent of all the anophelines reared from these inland collections. The remaining 1.2 per cent consisted of thirteen *quadrimaculatus*. The latter were all reared from static water while *punctipennis* alone was found in all the streams and springs examined. The streams were usually rather small, clean, with sand bottoms and a marginal fringe of green filamentous algæ. In this fringe *punctipennis* larvæ were always found, in numbers. Many were observed on the very edge of the algal margins, moving back and forth in the currents. On many occasions the larvæ were so numerous that they could easily be collected in a teaspoon. In a number of places, twelve to fifteen could be obtained in a single teaspoonful.

Summary

In considering the results of this preliminary survey, it should again be emphasized that it covered a period of only one month, beginning the 26th of August, 1939. The weather conditions were unusually favorable, the mean temperature for the month being 69.1, which was 6.6° F.

above the average. It did not fall below the freezing point during the month—a very unusual circumstance.

Under these conditions it is probable that the anopheline populations were at their peak. The situation is complicated, too, by the fact that the hibernation periods for the various species were approaching. No data were available regarding the early mid-season conditions.

The findings for the period of the survey, August 26 to September 25, may be summarized as follows:

1. Anopheline mosquitoes were found to be much more abundant in the Mississippi river valley, from Wabasha, Minnesota, to La Crosse, Wisconsin, than had previously been supposed.

2. Four species of anophelines already reported for Minnesota were found: *quadrimaculatus, walkeri, punctipennis,* and *maculipennis. Maculipennis,* which occurs commonly in northern Minnesota, was so rare as to indicate that it is of no significance in the survey area.

3. On the basis of building collections alone, where it constituted 91.7 per cent of the anopheline catch, *quadrimaculatus* would appear to be the most common species in the valley proper, while *punctipennis* with its 85.7 per cent was the most abundant inland. *Walkeri* was almost absent in these collections, although there is reason to believe that it may be the most common of the four.

4. In light trap collections in the residential district of Wabasha *quadrimaculatus* was present to the extent of 74.4 per cent while in the catches by traps located near extensive swamp areas at both Wabasha and La Crosse *walkeri* made up 67.7 per cent and 84.7 per cent, respectively, of the total anophelines.

5. In the small collection of anophelines attacking man in the open, *walkeri* was the dominant species. This is in agreement with observations elsewhere in Minnesota, and emphasizes the need for detailed studies on the biology of the species.

6. Anophelines were breeding abundantly throughout the valley in the extensive sloughs and backwaters. Larval collections yielded 57.4 per cent *quadrimaculatus* and 38.6 per cent *punctipennis* in these situations. Such evidence as is available indicates that *walkeri* oviposition is less concentrated but that it occurs in submerged grassy areas which are extensive in the region. An alternative is that the favorable season for larval development of the species had passd.

7. Data from collections from buildings, from light traps, hand catches, and larval collections revealed a surprisingly high incidence of anophelines, with *quadrimaculatus* and *walkeri* the dominant species. While there are no data relative to the abundance of these species prior to installation of the flood control dams, there is evidence that there has been a marked increase in favorable breeding places in the river valley for *quadrimaculatus* and apparently for *walkeri,* as well.

8. In the inland, in contrast to conditions in the river valley proper, *punctipennis* was the only anopheline found breeding in numbers. It constituted 98.8 per cent of the specimens reared from the inland collections.

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SCHIZOPHRENIA IN CHILDHOOD*

ROYAL C. GRAY, M.D., Ph.D.

Minneapolis, Minnesota

IN 1863 Kahlbaum isolated the mental disorder hebephrenia and in 1869 catatonia. Kraepelin, in 1896, united these two and the paranoid types into his concept dementia præcox and differentiated it from manic-depressive psychosis. As the disease does not always progress to dementia or appear precociously, at or soon after puberty, in 1911 Bleuler proposed the more accurately descriptive name schizophrenia. He considered a splitting and dissociation of the personality to be the fundamental symptom of the disease. Freud postulated that schizophrenia represents a fixation at the auto-erotic stage of development and is a narcissistic regression psychosis. Meyer regards schizophrenia as the reaction of a maladapted individual whose principal fault is a persistent misapplication of his instincts. Campbell[2] has defined the disorder as follows: "The schizophrenic type of reaction seems to be characterized by diminished interest in, and adaptation to, the work-a-day world, increased interest in subjective creations or phantasies which are emancipated from the control of ordinary logical or scientific thought, the frequent occurrence of hallucinations, odd and fragmentary behavior and utterances of little adaptive value in relation to the present situation."

The nervous system in the child is physiologically immature. His intellectual development and life experiences are comparatively limited. Therefore, Potter[9] states, children are essentially beings of feeling and behavior. Their language is restricted and hence they cannot fully verbalize their feelings. Consequently their psychopathology is expressed largely through distorted affective responses and altered behavior reactions.

All normal children live in their phantasies to a greater or lesser degree and the schizophrenic reaction is often likened particularly to the child at play. But according to Creak[4] these phantasies and vivid imaginations, ritualistic play, emotional instability, and other similar immature thought and conduct may be distinguished from a psychosis in the making by the early age of the patient, the temporary nature of the activity, and the fact that it may be understood. Manic-depressive psychosis in children is very rare indeed, arises only close to the time of puberty, and in the long run generally proves to be a schizophrenic reaction.

Cleland[3] maintains that the different types of schizophrenia have characteristic conduct disorders in childhood. Listless, lazy, tired-out attitude toward life presages the simple or hebephrenic type. Incoherent conduct and much activity without accomplishing anything foretells the catatonic type. But both prototypes may be characterized by irritability, periods of excitement and depression, mannerisms, and conduct peculiarities. Lutz[8] describes two types of schizophrenia in children, one slowly progressive without marked remissions and the other type often with catatonia, of rather sudden onset, and with definite exacerbations. However, any of these symptoms may be found in a normal child and differentiation of the various types of schizophrenia in children is practically impossible.

The schizophrenic is the odd, queer, or different child in the family and one is unable to really contact him. Richmond[10] says that in comparison the psychopathic child has some semblance of rapport and, furthermore, is cunning and possesses self-defensive instincts. He impresses one as capable if he would only apply himself whereas the schizophrenic impresses one as dull or defective. However, apparent dullness in a psychotic child is probably inattention due to his preoccupation rather than lack of comprehension.

The schizophrenic child may be differentiated from the mental defective by the fact that in the defective walking, and especially talking, motor coördination, and all learned reactions are greatly delayed. Consequently the psychotic child is likely to show some initiative even in devising varieties of his abnormal behavior. Finally, an intelligence test may provide a differential diagnosis between schizophrenia and mental deficiency. Lay[6] summarizes the differences as fol-

*From the Division of Nervous and Mental Diseases, University of Minnesota Medical School.

lows. In schizophrenia the patient shows scattering of responses through several age levels, does better on verbal than performance tests, does not react to urging or praise, improves on retest, and his intelligence quotient will not be noticeably low. In mental deficiency all these points are the reverse.

Schizophrenia is a psychosis of psychogenic origin without clearly defined tangible cause or structural change. Schilder[11] aptly emphasizes that pictures which resemble schizophrenia in childhood are very often schizoid reactions to organic processes or defects of the brain. Dementia precocissima and dementia infantilis, referred to in the foreign literature as forms of schizophrenia, really are not schizophrenia at all but primarily organic processes. Similarly, propf-schizophrenia is not a functional entity but rather is a schizoid reaction appearing in and incident to an oligophrenia.

The principal definite etiological factors in 151 cases of schizophrenia studied by Bowman and Kasanin[1] were environmental stress in 81 per cent and heredity in 64 per cent. It would seem that heredity does not predispose to any one type of psychosis but rather to an early mental breakdown. A primary psychic factor, a predisposition, may be the basis for mental disease; Jung termed an individual so conditioned to developing schizophrenia an introvert.

Schizophrenia constitutes about 25 per cent of all the psychoses. The number reported in childhood before the physical appearance of puberty is very small. The ages of those cases reported range from 3 to 16 years. Bleuler took 15 years as the dividing line and said 4 per cent of his cases had symptoms of schizophrenia before that age. Kraepelin, in 1913, reported a series of 1,054 dementia præcox patients of whom 3.5 per cent developed symptoms before ten years of age.

In about 6,000 admissions to the Boston Psychopathic Hospital from 1923 to 1925, Kasanin and Kaufman[5] reported that sixty-five under sixteen years of age were psychotics, of whom six were typically schizophrenic. Lurie et al[7] studied 1,000 children, ages eight to sixteen years, at the Cincinnati Child Guidance Home. These children were sent to the Home not because they appeared insane but because of failure to adjust either in their home, school, or community. Nineteen of these 1,000 children had a definite functional psychosis; thirteen of the nineteen were schizophrenic.

In 1,265 admissions of children under sixteen years of age to Maudsley Hospital, London, from 1935 to 1937, Creak[4] diagnosed thirty-five as functional psychosis. The author felt that practically without exception such a psychosis in childhood is schizophrenia and therefore did not subdivide these thirty-five cases.

In 5,000 consecutive admissions to the Pennsylvania Hospital Strecker[13] found eighteen functional psychotics under fifteen years of age. Of these, four were diagnosed schizophrenia, four doubtful, and ten manic-depressive psychosis.

In 32,443 hospital admissions in Munich from 1904 to 1922 Seelig[12] found 753 psychotics under fifteen years of age of whom forty-seven had been diagnosed schizophrenia. He questioned this incidence of schizophrenia and compiled the data in 23,935 admissions in Munich from 1922 to 1931 wherein he determined there were 480 psychotics under fifteen years of age of whom only four were schizophrenic. He also noted that during the same years of 27,377 admissions in Cologne 1,497 were psychotics under fifteen years of age but only three of these were schizophrenic.

During the ten year period from 1929 to 1939 there were 18,976 patients admitted to the three largest State Hospitals for the insane in Minnesota. Thirty-eight of these patients were under fifteen years of age and of this number eleven were diagnosed schizophrenia. The remainder had psychoses with mental deficiency, with epilepsy, with psychopathic personality, or with chronic encephalitis. Table I is a recapitulation of the incidence of childhood schizophrenia reported by various authors.

The prognosis in childhood schizophrenia is definitely unfavorable although not altogether hopeless. Kasanin and Kaufman[5] reported three of their six childhood schizophrenic patients continued in the hospital. In Creak's[4] series of thirty-five psychotic children, presumably all schizophrenic, twenty-six were traced, of whom fourteen improved and twelve remained ill. Potter[9] studied six schizophrenics, four to twelve years of age, all of whom showed symptoms before the age of ten. No one of the six had any improvement after periods of hospitalization of three to eighteen months.

All of the eleven schizophrenic children ad-

TABLE I. INCIDENCE OF CHILDHOOD SCHIZOPHRENIA

Author	Years	Place	Total Psychotic	Psychotic Children	Schizophrenic Children
Kasanin	1923-25	Boston	6,000	65	6
Lurie		Cincinnati	1,000	19	13
Creak	1935-37	London	1,265	35	35
Strecker		Philadelphia	5,000	18	4
Seelig	1904-22	Munich	32,443	753	47
Seelig	1922-31	Munich	23,935	480	4
Seelig	1922-31	Cologne	27,377	1,497	3
Gray	1929-39	Minnesota	18,976	38	11

TABLE II. PROGNOSIS OF CHILDHOOD SCHIZOPHRENIA

Author	Schizophrenic	Traced	Recovered	Improved	Unimproved
Kasanin	6	6		3	3
Creak	35	26		14	12
Potter	6	6			6
Gray	11	11	1	5	5

mitted to the Minnesota State Hospitals from 1929 to 1939 were traced. Four of these patients remain hospitalized after periods ranging from three to seven years. Table II is a recapitulation of the prognosis of childhood schizophrenia reported by various authors. It indicates that recovery is very rare and that over 50 per cent of these patients remain unimproved.

Table III has further data concerning these eleven Minnesota State Hospital patients. In this series the ratio of childhood schizophrenia in boys and girls is about 1 to 2, which agrees with previous observations. The types of the psychosis were distributed as follows: hebephrenic seven, catatonic two, and paranoid two. The only patient who recovered was one with the hebephrenic type. Of the remaining six hebephrenic patients, three improved and two are unimproved. One of this group (Case 6) was unimproved at the time of her death from bulbar palsy and progressive muscular atrophy. This organic neurologic disorder, which is most unusual in childhood, appeared about one year after her commitment to the state hospital. It indicates a marked abitrophy of the nervous system and suggests that schizophrenia and other functional psychoses perhaps in the final analysis may be structural in nature. Of the catatonic and paranoid patients one improved and one remains unimproved in each of these two types. One patient, a catatonic (Case 8), had two hospital

TABLE III. CHILDHOOD SCHIZOPHRENIC PATIENTS ADMITTED TO MINNESOTA STATE HOSPITALS.

Case No.	Sex M	Sex F	Admission Age, years	Type	Hospitalization Years	Hospitalization Months	Recovered	Improved	Unimproved
1	x		11	Hebephrenic		6	x		
2	x		14	"		3		x	
3	x		14	"	1	6		x	
4	x		14	"	3				x
5		x	13	"		6		x	
6		x	13	"	3				x
7		x	14	"	7				x
8		x	14	Catatonic		3		x	
9		x	14	"	3				x
10		x	14	Paranoid	2			x	
11		x	14	"	3				x
	–	–					–	–	–
	4	7					1	5	5

admissions, each of three months, with improvement in each instance. The other four patients who improved and the one who recovered were discharged from the hospital and have continued acceptably adjusted or well after periods ranging from two to seven years.

Schizophrenia in childhood is a rare and interesting mental disorder. Therefore the following report is presented concerning a patient affected with schizophrenia from nine years of age to his present age of twenty-four years.

Case Report

In September, 1930, M. M., a fourteen-year-old boy, was admitted to the University Hospital at the request of his paternal grandfather. His mother was residing in Colorado, and the whereabouts of his father was unknown. The history which the grandfather was able to furnish was very sketchy. The principal informant was the boarding mother, a trained nurse, with whom the patient had been living much of the preceding five years.

The father's age was forty years, the mother's thirty-two. Her health was good. The patient was an only child. His parents were divorced when he was about six years of age. Thereafter for two years he was in an orphange, for one year with his mother, and then, in 1925, was placed in the informant's home.

The boarding mother said when the patient first came to live with her he would sneak about and appeared to be afraid. He was a peculiar and imaginative child. He would have frequent temper tantrums. He had piano lessons for three years and made very good progress. He was honest and trustworthy in all respects. He was always neat and polite. He was a member of a local Boy Scout troop, but never seemed to get into the spirit of the organization. He was

unduly sensitive and did not want to play with his schoolmates because they teased him for being timid.

After school hours he would stay in the house reading or writing poems, the subject matter of which frequently was in reference to religion or to a boy without a home. It was difficult to draw him into conversation, and one practically had to ask him a question in order to get him to say anything. In answering he would never talk directly to one but would turn away and look out of the window or he would stare into space for a while before replying.

A year previous to his hospital admission he spent one week with his father. He ran away from his father, returned to the informant's home, and said he had been mistreated. For three months previous to his hospital admission he had been living with his grandfather, who, according to the informant, was an overly religious individual.

The boy had completed the seventh grade in public school. His sixth grade teacher said he was peculiar in many ways and subject to a violent temper. Once when she reprimanded him he became very angry and shouted for a gun to shoot her. He was a superior student, especially in arithmetic and reading. In written work he was somewhat slow but very thorough. His seventh grade teacher said he did passing work in all his subjects, but was inclined to be a dreamer. He never seemed interested in playing with the other children unless he was in the right mood. He was slow in working with his hands. He excelled in writing original stories as he had an unusual imagination. The following poems, taken from his composition book, clearly show his trend of thought.

My Mother

I walk upon the rocky shore
Her strength is in the ocean's roar
I glance into the shaded pool
Her mind is there so calm and cool.
I hear sweet rippling of the sea
Naught but her laughter 'tis to me.
I gaze into the starry skies
And there I see her wondrous eyes.
I look into my inmost mind
And here her inspiration find.
In all I am and hear and see
My precious mother is with me.

Sweet Death

When at last your tired eyes close
No more to witness earthly woes
No more your struggle against cruel life
Which is only filled with tears and strife.

As far as could be learned the family and personal histories were negative. The boy said for six weeks he had been disturbed about his past evil acts and his present bad thoughts. He said he had heterosexual experiences when he was nine or ten years of age, his nerves were now hurting him, and he had funny ideas. He complained of weakness, headache, indistinct vision, heartburn, generalized gastric discomfort after eating, and tingling in his hands and feet. He said he had trouble in breathing, that he breathed too much with his stomach and not enough with his chest. He could not sleep well and was disturbed by distressing dreams.

The general physical and neurologic examinations and the routine laboratory tests all were negative.

His attitude and general behavior were variable. Some days he was quiet and well mannered and helped with various chores around the wards. Often he had outbursts of unusual activity such as violently rocking forth and back in his chair or pacing excitably about the room pushing chairs from place to place. He would shout about God and the devil and talk disconnectedly frequently about snakes. At times he would strike the wall and beat himself. He would throw whatever might be at hand and mechanical restraints were sometimes necessary.

Other days he appeared depressed, cried considerably, and remained in bed. He said he did not want morning to come because it would be just another day. Sometimes he walked with a peculiar limp. He had spells wherein he seemed to have considerable difficulty in breathing.

He talked much about religion, the end of the world, and politics, and lectured to fellow patients on these subjects. Sometimes he went from patient to patient telling them they only imagined they were sick.

Most of the time he was uncommunicative, stared fixedly and without expression at some object, and appeared to be out of contact with his surroundings. There was commonly a long pause before he had any answer; whatever reply he made was disconnected and contained pronouns without antecedents. Sometimes he read in a loud voice from a book, usually starting at the back of the book. He said that no one understood him and everyone was talking about him. Then he would say he was disgusted with the Bible—"It's no good, I'd sooner play cards." He would mutter under his breath, repeat words and phrases several times, slam doors, and say he was going to kill himself by taking poison or jumping out of the window.

Some days he carried an apparently useless article, such as a roll of newspaper, around with him. He would snatch at space and say he saw little white things. He developed periods of silly laughter. He was suspicious of black-haired persons and said their purposes could not be defeated. He would put his bathrobe on backwards, did not understand how to put on his bedroom slippers, and stumbled awkwardly as he walked. He continually heard people say he was not a real boy. He often spoke of the sound of rain falling out of doors.

As time passed he became disoriented, his memory for remote and recent events poor, and his retention and recall lost. His grasp of general information became progressively more inaccurate. His insight and judgment failed.

He became very noisy, incontinent, and would not eat. He finally became so difficult to manage that he was transferred to the State Hospital in December, 1930.

The symptomatology in this case of autistic thinking, preoccupation, negativism with no basic mood disturbance, episodes of excitement, bizarre behavior, and mental regression warranted a diagnosis of schizophrenia, hebephrenic type.

The patient was unsuccessfully paroled from the State Hospital to his grandfather from May to August, 1931. In August, 1932, he was again paroled, this time

to his mother. He ran away from her home, was apprehended in Pennsylvania, and returned to the hospital in January, 1933. He eloped from the hospital in April, 1935, and was subsequently paroled to his mother in June, 1935. During a part of the next two years he was employed and rather interested in his work. However, disabling symptoms of the psychosis reappeared and in September, 1937, he was returned to the Hospital, where he has since remained.

His present mental status is as follows: At times he becomes very disturbed and peculiarly manneristic. He is careless about his personal appearance and generally is preoccupied. He appears apathetic, indifferent, and somewhat depressed. He does not initiate any conversation and answers only fragmentarily. He has aural and visual hallucinations and persecutory delusions. He is oriented for person and place but not for time. His remote memory is fairly good; recent memory is poor. His calculations are slow but accurate. His grasp of general information is moderately deficient. His insight and judgment are severely impaired.

Summary

The incidence of schizophrenia at whatever age obviously varies somewhat with the diagnostic criteria employed. Approximately one in 400 cases of schizophrenia manifests itself in childhood. The prognosis of childhood schizophrenia appears poor; recovery is an exception and improvement occurs only in about one-half the cases.

The fourteen-year-old boy here reported was diagnosed as schizophrenia, hebephrenic type. The symptoms of the psychosis were evident from the age of nine years. He remains unimproved at age of twenty-four. His pre-psychotic personality was that of an introvert. There is no known hereditary or constitutional factor involved in this case. The patient's conduct and writings indicate that environmental stress incident to the broken home was likely the precipitating factor in his psychosis.

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ERYTHROBLASTOSIS (ICTERUS GRAVIS) IN THE NEWBORN

Report of a Family of Three Children

JOHN M. ADAMS, M.D., and RAY F. COCHRANE, M.D.
Minneapolis, Minnesota

ALTHOUGH confusion prevails as to the existence of erythroblastosis fetalis as a definite clinical entity, severe icterus and edema of the newborn occur not uncommonly and require immediate treatment if life is to be preserved. We are calling attention to a family of three children: the first child died two hours after birth; the second child developed a typical picture of erythroblastosis and lived following treatment; the third child is perfectly normal, the mother having been treated during pregnancy with liver extract.

The highly familial tendency in this disease is well recognized. The possibility that many still-births or premature deaths are cases of erythroblastosis, unrecognized, is a point which needs a great deal of emphasis. Javert[3] and Macklin[4] have both emphasized this fact. Bleeding or evidence of hemorrhage at necropsy following a difficult delivery may often be listed as the cause of death. This was the situation in the first case here reported. Only by the more careful and frequent examination of the viscera at necropsy in these babies will the true incidence and cause of death be revealed.

The prognosis of erythroblastosis heretofore has been very unfavorable. In the presence of universal edema of the newborn, death always results.[6] When icterus is associated with edema, there have been a few recoveries. Three such

cases have been reported by Diamond, Blackfan and Baty in the literature.[1] Pehu[5] believes the disease occurs more frequently than previously recorded and reports several families in which eight to nine pregnancies are recorded with but a single living child. He states that the disease can occur without the presence of numerous nucleated red cells being present in the peripheral blood, the only positive diagnostic evidence being found in the bone marrow and visceral organs. Pehu further states that in cases of previous evidence of erythroblastosis in the family, it is the duty of the physician to treat the mother during pregnancy with liver extract and transfuse the baby immediately following birth.

The early diagnosis of this condition is vitally important. The presence of an edematous placenta as well as a deep yellow amniotic fluid and vernix caseosa will greatly facilitate diagnosis. Jaundice usually appears in twelve to twenty-four hours following delivery. Pallor or anemia is an important feature but may be masked by the deep yellow color of the skin. The spleen and liver are enlarged. The blood picture usually shows a large number of erythroblasts and immature forms of both the red and white blood-cell series, the nucleated red cells averaging 20,000 to 100,000 per cubic millimeter. Anemia is striking and the hemolytic feature is outstanding, as manifested by increasing jaundice and anemia in spite of frequent transfusions. The van den Bergh is invariably indirect.

The differential diagnosis involves the following: congenital syphilis, sepsis of the newborn, congenital biliary obstruction, icterus neonatorum, acholuric jaundice and erythroblastosis fetalis,[7] which includes icterus gravis, erythroblastosis, leukoblastosis and edema associated with icterus. Because of the bleeding tendency in some cases, hemorrhagic disease of the newborn should be included in the differential diagnosis.[8]

Pathologically the disease is one of diffuse erythropoiesis. The liver shows large numbers of hematopoietic areas scattered throughout the parenchyma. There is hyperplasia of the spleen, kidneys, heart, pancreas and bone marrow.

The following family is reported to emphasize the importance : (1) of the familial nature of this disease; (2) complete diagnosis in stillbirths and deaths attributed to difficult delivery; (3) the importance of early diagnosis and immediate treatment by multiple transfusions; (4) the importance of the possibility of preventing the disease by treating the mother throughout pregnancy with parenteral liver extract. This suggestion was first made by Pehu,[5] in the French literature. The third pregnancy reported here was treated throughout with parenteral liver extract. The baby is perfectly normal. This is offered merely as a suggestion worthy of further trial in families where the disease is known or even suspected to exist.

Case 1.—The mother is a twenty-one-year old primipara. The last menstrual period was July 5, 1936. She had no toxic symptoms during her pregnancy and had received regular prenatal care. Labor commenced May 1, 1936, and after five and a half hours a male infant was delivered, footling presentation. There was some difficulty in extracting the after-coming head.

The condition of the baby was poor and he died two hours after birth, all of the usual methods of treatment having been employed. The findings of significance at necropsy were as follows: Birth weight 9 lbs. 11 oz.—4400 grams, liver weight 130 grams (normal 70-88 grams). No gross edema was noted. There was a cephalhematoma in the left temporoparietal region about the size of a hen's egg. There was hemorrhage over both cerebral hemispheres and blood at the base of the brain.

Diagnoses: (1) Cerebral hemorrhage; (2) Cephalhematoma.

Microscopic examination of the liver and spleen revealed a normal appearing tissue containing several blood islands, but appeared to the pathologists to be within normal limits for a newborn. The spleen showed hyperplasia. Bone marrow study was not done.

Clinically this patient might conceivably be classed as a case of erythroblastosis, the weight of the baby being in excess of the average newborn and over 2 pounds heavier than her subsequent children at birth. The liver weight of 130 grams was about two times the average weight of the liver of the newborn. The cephalhematoma and cerebral bleeding indicated an abnormal bleeding tendency, occasionally seen as a clinical feature of erythroblastosis.

Case 2.—The second pregnancy was normal throughout and resulted in a female child born following a normal delivery on August 4, 1937. The birth weight was 7 pounds 5.5 oz. (3300 grams). The baby appeared slightly pale and sallow at birth, but otherwise normal on examination.

About twelve hours following delivery, definite jaundice was noted and physical examination at that time revealed an enlarged spleen, palpable 3 cm. below the costal margin. The liver was not felt at that time.

The stools were dark brown in color and gave a positive test for bile. The urine was also dark in color with a positive test for bile pigments. The hemoglobin was 80 per cent or 13.6 grams (Sahli) (normal 110), white blood cell count 31,000, Kline test for syphilis negative.

The report of the hematologist on August 6 was as follows: "The blood smear shows the following morphological features: Anisocytosis of considerable degree, numerous macrocytes, polychromasia and many nucleated red blood cells. Most of these appear to be macro-normoblasts, and a few cells have many features consistent with megaloblasts. There is a shift to the left in the myeloid line all the way to stem cells which may be found with relative ease. I do not believe this may be said to constitute a leukemia on the bases of the present findings, but rather a leukemoid reaction."

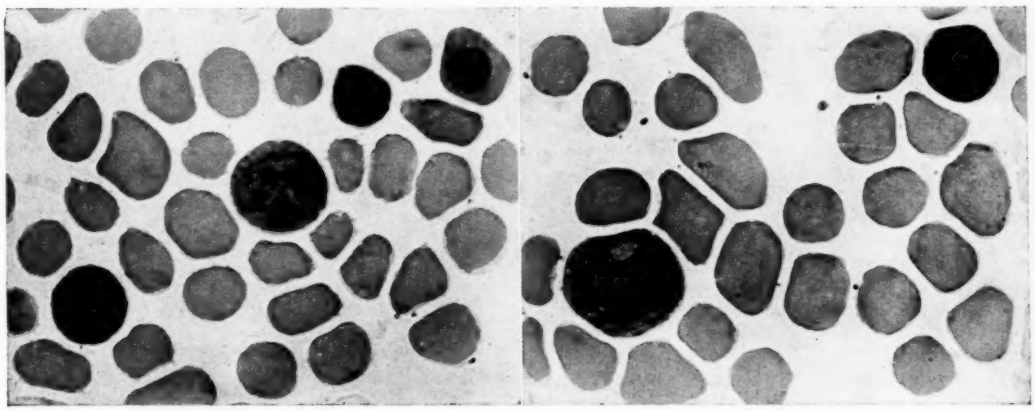

Fig. 1. Stained blood smears, Case 2, showing microcytosis and macrocytosis, immature red blood cells, normoblasts and macro-normoblasts, and immature white blood cells (oil immersion).

Blood smears taken on August 5 revealed a large number of immature red blood cell forms of the normoblast series, over 50 per cent of the nucleated cells being of this series. The differential white blood count revealed myelocytes 9 per cent; metamyelocytes 7 per cent; polymorphonuclears (I) 2 per cent; polymorphonuclears (II) 23 per cent; polymorphonuclears (III) 36 per cent; lymphocytes 22 per cent; monocytes 1 per cent.

Except for a temperature elevation to 100° F. (rectal) on the second day of life (August 5) the course was entirely afebrile.

On August 6 a transfusion of 80 c.c. of citrated blood from the father was given. The hemoglobin following this procedure was 89 per cent or 14.8 grams (Sahli). Cevitamic acid was started, 50 mg. daily being given orally throughout the hospital stay. Progress was favorable although evidence of hemolysis continued. The jaundice became intense and the spleen remained readily palpable, 3 cm. below the costal margin.

On August 9 the hemoglobin was 76 per cent or 12.8 grams (Sahli), and a second transfusion of 90 c.c. of citrated blood was given.

On August 12 the hemoglobin was 34 per cent or 5.6 grams (Sahli), and a third transfusion of 80 c.c. of citrated blood was given. Following this procedure, on August 13 the hemoglobin was recorded at 69 per cent or 11.6 grams (Sahli). The red blood cell count was 3,460,000.

On August 14, 1 c.c. of concentrated liver extract was given intramuscularly.

On August 15 the spleen was definitely smaller, being barely palpable, and the patient was sent home on iron medication only.

On September 3, 1937, four weeks after birth, the hemoglobin was 50 per cent or 8.4 grams (Sahli), reticulocytes 10.1 per cent. In spite of the evidence of active hematopoiesis, the hemoglobin was 52 per cent or 8.6 grams (Sahli) on October 2, 1937. One month later, on November 2, the hemoglobin had risen to 68 per cent or 11.6 grams (Sahli). The tip of the spleen could still be felt. On January 4, 1938, the hemoglobin was 92 per cent or 15.6 grams (Sahli). The spleen was no longer palpable. On March 1, 1939, the hemoglobin was 85 per cent or 14.4 grams (Sahli) and on May 9, 1938, it was 91 per cent or 15.4 grams.

One year following birth the physical examination was negative. The hemoglobin at this time was 82 per cent or 13.8 grams (Sahli). The child's development is normal, physically and mentally. At two years of age the patient is perfectly normal.

The above case seems to be rather typical of erythroblastosis fetalis, the striking features being pallor at birth, jaundice twelve hours later, increasing in severity for several days. The spleen was markedly palpable. The blood picture contained all of the characteristic features, large numbers of erythroblastic as well as leukoblastic cells.[6] The response to multiple intra-

venous transfusions was very favorable. The importance of giving whole blood early cannot be overemphasized. Blood grouping and cross matching should always be done regardless of the patient's age or the use of parental donors.

Case 3.—The third pregnancy was normal throughout. The mother was given concentrated liver extract intramuscularly the last seven months of pregnancy at monthly intervals. X-ray examination of the mother was made in accordance with the technic outlined by Hellman and Irving,[8] and failed to reveal any thickening or increased density of the soft parts of the fetus, indicative of edema. On September 14, 1939, a normal baby was born, weight 8 pounds 6 ounces. Examination revealed a normal newborn baby infant. The blood picture was as follows: hemoglobin 120 per cent, red blood cells 5,000,000, white blood cells 27,600, polymorphonuclears 64 per cent, lymphocytes 32 per cent, eosinophiles 4 per cent, bleeding time 3 minutes 30 seconds, clotting time 4 minutes. The smear showed no abnormality. At the age of six months this patient is quite normal.

Conclusions

1. The importance of complete and accurate diagnosis in all cases of still-births is again emphasized.

2. Treatment by multiple intravenous transfusions offers the greatest hope of cure in cases of erythroblastosis. Ascorbic acid and liver extract was also used in Case 2.

3. The possibility of preventing this disease by the administration of parenteral liver extract to the mother during pregnancy is merely suggested. The result of the third pregnancy in this family following liver therapy was normal.

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THE SULFAMIDO COMPOUNDS: THEIR PRACTICAL APPLICATIONS IN CLINICAL MEDICINE*

ALEX E. BROWN, M.D.
Rochester, Minnesota

THE present importance of sulfamido therapy as well as the rapidity with which this field has developed suggests the advisability of reviewing certain practical phases of this subject. It is true that our knowledge is still incomplete in many respects but it is also true that experience has taught us certain factors which serve to distinguish between adequate and inadequate therapy. I wish to discuss what I believe to constitute some of these factors.

Fundamentally, we have available only four sulfamido drugs of proved clinical value, namely neoprontosil, sulfanilamide, sulfapyridine and the sodium salt of sulfapyridine.

With this number of compounds to choose from it is necessary to use care in selecting the one most suited for the infection to be treated. There are several factors of importance which enter this decision. 1. Marked variability in absorption and acetylization of sulfapyridine. It is possible because of this factor to give a large amount of sulfapyridine without obtaining a satisfactory concentration of the free drug in the blood. On the other hand, with the use of sulfanilamide it is usual to obtain a concentration of that drug in the blood which is fairly closely related to the amount given. 2. Sulfapyridine appears to be a more toxic preparation than sulfanilamide. It produces all of the toxic effects of sulfanilamide and in addition shows an increased tendency to produce nausea and vomiting. It also may give rise to renal complications. 3. Neoprontosil while less toxic than sulfanilamide, is also proportionately less effective therapeutically. Neoprontosil thus lends itself for use particularly in instances in which sulfanilamide is not well tolerated and in which prolonged or intermittent treatment is indicated. It is also of value in circumstances in which it is not possible to keep the patient under close observation dur-

*From the Division of Medicine, The Mayo Clinic, Rochester, Minnesota. Read before the annual meeting of the Minnesota State Medical Association, Rochester, Minnesota, April 22, 1940.

ing treatment. 4. The individual drugs vary in their therapeutic effect on specific types of organisms.

Sulfanilamide to date, because of the foregoing reasons, is the drug of choice for infections produced by the beta hemolytic streptococcus. This is true of localized lesions and of more widespread infections such as septicemia and meningitis. In cases of hemolytic streptococcus septicemia, Herrell and I have found in a recent unpublished review that the mortality rate at The Mayo Clinic has dropped from 70 per cent to less than a half of that figure since the use of sulfanilamide was instituted. Sulfanilamide is probably also the drug of choice for infections produced by gonococci, although the controversy in regard to its merits and those of sulfapyridine for this condition is as yet unsettled. For infections involving the urinary tract, I should feel that, in general, sulfanilamide is also the drug of choice. Finally, infections produced by meningococci and by Clostridium welchii are members of the group of conditions preferably treated with sulfanilamide.

Sulfapyridine is definitely the best sulfamido drug for infections produced by pneumococci. The question as to the respective merits of sulfamido versus serum therapy for pneumonia is as yet unsettled and time will permit us only to touch briefly on this subject. It is necessary to bear in mind that the fundamental approaches of each of these methods of treatment are essentially different from one another. Serum acts by throwing an increased number of specific antibodies into circulation which neutralize capsular substance and thus permit phagocytosis and lysis of the organisms. Sulfapyridine reduces the multiplication of organisms and diminishes their invasive power and thus permits a normal number of antibodies to overcome weakened organisms which are diminished in numbers. It can be seen that for these reasons there is a basis for a synergistic action of serum and sulfapyridine such as has been described by Branham and Rosenthal and by MacLeod among others. Because of this the combined use of these two methods of treatment is justified for the severely ill patient when specific serum is available. In considering the problem it is necessary to take into consideration the cost of serum, plus the necessity for typing with its delays, as well as the availability of specific serum. Experience has shown that the results of sulfapyridine therapy compare very favorably with the results of serum therapy. With all of this in mind it seems reasonable to start immediate treatment with sulfapyridine in cases of pneumonia and to carry out typing simultaneously. The sodium salt of sulfapyridine should be given intravenously, initially, for the acutely ill patient or may be given within a period of twenty-four hours if satisfactory improvement does not occur or if a satisfactory concentration of the drug in the blood is not obtained.

Sulfapyridine is the preferable drug for infections produced by the Staphylococcus aureus, Friedlander's bacillus and the Streptococcus viridans. Because of the effect of this drug on the beta hemolytic streptococcus it is also the drug of choice for infections of unknown etiology.

There is a second group of conditions aside from the foregoing in which the results from sulfamido therapy are not entirely satisfactory but appear to be of some benefit. Included in this category are such conditions as trachoma, lymphogranuloma inguinale, chancroid, undulant fever, and chronic ulcerative colitis.

Acute rheumatic fever, chronic infectious arthritis, subacute bacterial endocarditis, tularemia and the virus infections constitute a third class of conditions which definitely have failed to respond to sulfamido therapy.

The question of proper dosage is next in importance to that of selection of the most suitable drug, for failure to give a sufficient amount of the drug ranks equally with overdosage as a serious error of judgment. Good therapy requires the presence of an adequate concentration of the drug in the blood as soon after treatment is started as is possible. In using sulfanilamide for infections of moderate severity, concentrations of 5 to 8 mg. of the drug per 100 c.c. of blood are usually sufficient and ordinarily can be obtained in adults by giving 60 to 90 grains (4 to 6 gm.) of sulfanilamide daily. For mild infections and infections of the urinary tract concentrations of 3 to 5 mg. of the drug per 100 c.c. of blood will usually give satisfactory results and can be obtained in adults by giving 40 to 60 grains (2.7 to 4 gm.) of sulfanilamide daily. In the foregoing two groups of infections, there exists a frequent tendency to give more drug than is necessary. This, of course,

often results in symptoms of toxicity which disturb the patient and at times make it necessary to discontinue treatment before recovery has taken place. In using sulfapyridine for such infections as pneumonia, it is best to have a concentration of 4 to 6 mg. of the drug per 100 c.c. of blood. Usually an initial dose of 60 grains (4 gm.) and a daily maintenance dose of 90 grains (6 gm.) will result in such a concentration in adults.

The grave error of insufficient dosage usually is made in dealing with serious infections such as bacteremia and meningitis. For these conditions, there is a frequent tendency to give too little drug initially. The tendency is then to increase gradually the amount of the drug given as the situation grows more serious until in the terminal stages of the disease the patient as a last resort receives amounts of the drug approaching those which should have been given initially. Lockwood aptly expressed the effect of sulfamido therapy when he stated that the best results were obtained in the presence of maximal invasion of tissue and minimal destruction of tissue. He also produced experimental evidence to show that increased destruction of tissue causes increased formation of peptone which in turn seems to inhibit bacteriostasis. For these reasons, it is essential in cases of bacteremia and meningitis to obtain high concentrations of sulfamido drugs in the blood as soon as is possible in order to combat the infection before it can be well established in scattered regions and produce increased destruction of tissue. Experience has shown that treatment of this type will definitely lower pre-existing mortality rates. It has also shown that any tendency to lower these high concentrations of the drug before recovery is complete will definitely result in prolonged periods of morbidity. In using sulfanilamide for these conditions it is advisable to obtain a concentration of 12 to 16 mg. of the drug per 100 c.c. of blood. In using sulfapyridine for bacteremia associated with pneumonia, the concentration of the drug in the blood should be 10 to 12 mg. per 100 c.c. In cases of Staphylococcus aureus septicemia, the concentration of sulfapyridine in the blood should be 16 to 18 mg. per 100 c.c.

In using the sulfamido compounds it is essential that these high concentrations be established by the initial dose and that subsequent doses be directed at maintaining the concentrations thus obtained. In using sulfanilamide, this type of result can usually be obtained by giving an initial dose of 50 to 80 grains (3.3 to 5.3 gm.) of the drug to adults, depending on the patients' weight.

In order to obtain the desired high concentration of sulfapyridine in the blood, it is frequently necessary to supplement oral administration with the intravenous use of the sodium salt of sulfapyridine. As a rule, we have given 0.06 gm. of the sodium salt of sulfapyridine per kilogram of body weight as originally suggested by Marshall and Long. At times we have given amounts greater than this but in no instance have we given more than 5 gm. of the sodium salt of sulfapyridine in a single dose. We have dissolved this material to make up a 5 per cent solution in distilled water. As this solution is highly alkaline it must be given directly into the vein and must be given slowly. The dosage suggested will usually serve to increase the concentration of the drug in the blood by 5 to 8 mg. per 100 c.c., and the dose may be repeated in six hours if desired. It is to be emphasized that this form of intravenous medication is to be used essentially as an adjunct to oral therapy and in instances in which oral therapy will not produce the desired concentration of the drug in the blood or where it is desired rapidly to produce this desired concentration. We have used it only in rare instances as the sole measure of treatment. It is well to remember that if the patient is unable to swallow, sulfapyridine may be given as a suspension in milk or water through a Rehfuss tube. The sodium salt of sulfapyridine in a 5 per cent solution should never be given intramuscularly or subcutaneously and sulfapyridine should never be given intravenously.

In conjunction with treatment I would like to emphasize that it is possible to commit a serious error in the treatment of some conditions by discontinuing the use of the drug too soon. Recurrences of disease are particularly likely to occur if infections are produced by staphylococci or pneumococci, or in cases in which the lesion involves the ear, bone, meninges or blood stream. In the presence of infections of this type, it is well to continue with some administration of drug for six to ten days after recovery has apparently taken place.

The toxic effects which result from the use of these compounds are too generally well known to bear a systematic review at this time. There are, however, certain points connected with these toxic effects which are of sufficient importance to be briefly emphasized. Among these are such facts as: 1. Cyanosis is probably the most prevalent and impressive of toxic symptoms but is of least importance as an indicator of danger. 2. Acute hemolytic anemia tends to occur in the first week of treatment and a mild progressive anemia may occur later. 3. Leukopenia and agranulocytopenia tend to occur after the first week of treatment. 4. Cutaneous eruptions and fever tend to occur particularly in the seven to eleven days of treatment. 5. Persistent mild symptoms of toxicity may offer a warning of more serious impending complications and should be carefully heeded. 6. When high concentrations of drug are present in the blood it is necessary to observe carefully for possible renal complications or cerebral manifestations of toxicity.

It has been our experience to learn that increasing observance of the foregoing principles has resulted in a definite improvement in the results which we have obtained with infections treated with sulfamido compounds.

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◆ CASE REPORT ◆

THREE VARIANTS OF SOLITARY RENAL CYSTS*

ARNOLD SCHWYZER, M.D.

Saint Paul, Minnesota

THREE cases of solitary renal cysts are herewith reported which illustrate variations in their site and relation to the kidney and pelvis and also as to their pathogenesis.

Case 1.—Mrs. T. St., a woman fifty-five years old, had had seven children, but no serious previous illnesses. For about a year she had often suffered from nausea and intestinal pain. Some months before coming to us she had had repeated vomiting but never any severe attacks of pain. She had lost some weight. She was referred to us on account of a large mass in the left hypochondrium, which was sensitive and extended from the kidney lodge to below the navel and almost to the midline. Bilateral retrograde pyelograms were made. The right side appeared normal. The left kidney shadow was found markedly enlarged, the inferior pole extending down almost to the iliac crest. Evidence of considerable pressure on the inferior portion of the left renal pelvis was noticed and also on the inferior calix which was markedly dilated and had lost the terminal markings. The left ureter was displaced mesially. The appearance indicated a large mass in this region which could be either a large tumor or a cyst. The absence of invasion of the inferior calix made the roentgenologist decide, though not definitely, in favor of a cyst.

At operation a cyst as shown in the sketch (Fig. 1) was found. It was the size of a very large grapefruit (11 cm. in diameter). After freeing the cyst, a sling, made of gauze, was placed around it and with this help the mass which was almost too large for the wound could be brought to the surface. The upper pole of the kidney was left undisturbed. The lower pole of the kidney from which this cyst originated, was then resected and sutured step by step. The report of the operation reads that less than a teaspoonful of blood was lost in resecting the kidney. Recovery was uneventful. There is nothing particularly noteworthy about this case except that the cyst is the largest of this kind I happen to have seen.

Case 2.—Mrs. St. Gl., on February 16, 1937, came to our office where the following notes were made: Age thirty-five, had three children living and well. Had thyroidectomy in 1926 and tonsillectomy six weeks later.

For four days pain had been frequent in the right iliac fossa. Eating caused cramps and no appetite was present. Bowels have been regular.

Examination of the decidedly nervous person yielded no evidence of disease of the head, neck or chest. The upper abdomen was normal, the cecum bulky and was the seat of the pain. The right kidney was very loose; it could readily be brought far over to the midline and downward to rest with its midportion over the innominate line. The pain was, however, not located in the kidney. A bulky hump could be felt on the kidney and two sketches were made which showed that we were uncertain whether the rounded prominence rose from the midportion (Fig. 2) or the upper pole. The x-ray showed a distorted middle calix and no filling of the lower one. The urine was normal. After a transfusion on account of marked anemia, we first removed the long and thickened appendix through a small gridiron incision. Before closing the wound we had the

*Demonstrated before the Saint Paul Surgical Society, March 7, 1940.

patient draw a deep breath which brought the kidney down where we could hold it over the innominate line. We then saw on the kidney a bluish round bulging, the size of a tangerine, distinctly a cyst. A lumbar incision of 4 or 5 inches, half of which was over the lumbar muscles, was made and through the anterior half

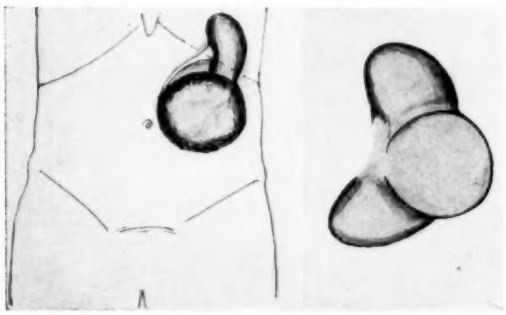

Fig. 1 (left) Case 1. Large cyst of lower pole.
Fig. 2. (right) Case 2. Cyst over posterior aspect of midportion of kidney.

of it the flat abdominal muscles were simply split. We did not feel we needed much of an opening. However the costo-vertebral ligament was cut. Through this restricted incision the kidney could not be brought out of the wound but with the help of a rubber tube looped around it, was brought sufficiently into the wound to excise the cyst which proved to be sitting on the midportion of the posterior surface. Considerable urine escaped from the pelvis of the kidney. However, the cyst was not opened. It was cut away with a very thin layer of kidney parenchyma. A continuous catgut suture controlled the bleeding. The hemostasis was assisted by Sistosan. The ptosis was counteracted by the insertion of four rubber drains. It is now nearly three years and there are no complaints referable to the kidney though the patient is of a highly neurotic type. The cyst, which you see here, has a diameter of about six centimeters.

The patient had herself felt the floating kidney and had been worrying about it. What symptoms there may have been, were due rather to the pulling on the renal pedicle than to the harmless looking cyst.

Case 3.—A para-and intercalicinal cyst of kidney. The patient, Dr. A. W., a woman of sixty-five years, had spent twenty-three years as a missionary physician in upper India. She had been of robust physique but went through most strenuous years being the only scientifically trained doctor in an area 150 miles long and 50 miles wide, doing all kinds of medical and surgical work, neglected appendices, gallbladders, goiters, hysterectomies, cesarean sections, bone operations and what not, with several hundred cataract operations thrown in for good measure. In the course of years she had undergone an appendectomy, hysteromyomectomy, but always afterwards resumed her work. However, about five years ago she was forced to give up when she was taken with a severe hemorrhage at the base of the brain. In 1938 a profuse hemorrhage from a duodenal ulcer occurred and in addition to all this she was suffering from a moderate diabetes and high blood pressure (210/102).

She came to me primarily on account of a severe and constant pain in her right hand where the index finger had been removed on account of a septic infection thirteen years before. Excision November 15, 1939, of a neuroma of a branch of the median nerve and resection of a tendon to which the neuroma was fixed gave such prompt relief that she had the courage a few days later to tell me of a constant great pain in the left kidney region. Palpation of the kidney area was very painful. The kidney itself appeared somewhat enlarged. The sugar in the urine had cleared up after a few days of strict diet. Blood urea 42 and 24 mg. on two occasions. Phenol-sulphone-phthalein test yielded for the first hour 30 per cent and for the second 15 per cent.

X-ray study before and after the intravenous injection of Diotrast showed an enlargement of the upper pole of the left kidney (Fig. 3). A rounded pressure defect on the upper part of the pelvis was seen which also caused an elongation of the lower calices. In addition the roentgenologist (Dr. Medelman) saw evidence of marked pressure on the upper calices. The right side appeared normal.

On November 20 we exposed the left kidney under spinal anesthesia. A most severe perinephritis was encountered, the kidney being firmly adherent to the hardened cicatricial fat. Caution forced us to deliver the kidney only partially into the wound on account of the cicatricial fixation of the pedicle. The sketch demonstrates the appearance of a cyst resting broadly against the posterior aspect of the renal pelvis. It was very thin walled, bluish, and if it had not been for the great thinness and transparency of its wall, could have been taken for a distended pelvis on account of its relation to the kidney. It then ruptured and was widely opened, which allowed us to recognize its peculiar relation with the pelvis, the bulk of which ran freely through the center of the cystic cavity and was considerably elongated. The calix leading to the upper pole was greatly drawn out. It ran freely through the lumen of the cyst cavity and could be hooked over the finger. It was hardly bigger in its midportion than a parlor match, (2.5 to 3 mm.). The portion lying free in the cavity was 3 to 3.5 cm. in length. It was seen emerging from the main portion of the pelvis which was also for the greatest part of its circumference in the cavity of the cyst.

We had the impression that a thin-walled cyst had developed in or very near the space between the upper main calix and the main portion of the pelvis, perhaps near the surface of the columna Bertini, corresponding to this interspace. The cyst would then have separated the parts, grown in where the resistance was least, encircled the upper calix completely and almost completely the remainder of the pelvis. The cyst walls where they touched each other after surrounding the upper calix, must have disappeared, an occurrence one sees quite commonly for instance in multilocular ovarian cysts where parietal remnants of such septa tell the tale.

It did not appear proper to stretch the parts too much for further investigation for fear of incurring damage. The free parts of the cyst wall were resected and the remainder swabbed with absolute alcohol. Collapsible rubber drains were put in place and the wound closed, after a pea-sized cyst on the surface of the cortext had been punctured. The patient left the hospital on the eighteenth day. The wound then slowly closed. In a letter dated January 15th, the patient reports that the old pain was gone. How much of the distress had been due to the cyst and how much to the severe perinephritis remains questionable. A later report announced again much pain in that area.

The microscopic examination of the cyst wall showed only thin strands of connective tissue. No lining, neither epithelium nor endothelium, was seen.

To sum up:

The first case was a solitary cyst of the type most frequently seen but unusually large.

The second one was located in the midportion of the kidney and had an intimate connection with the renal pelvis.

The third case appears to be quite unusual on ac-

count of its extending in between the calices and also by the absence of any epithelium which otherwise lines these cysts. A parasitic cyst, like an ecchinococcus, could definitely be excluded, though exposure to tropical filth and poverty leads the thoughts in such a direction. There remains the possibility of lymphatic origin or of some infective process leading in the late end to a local hydropic condition. This latter view would be supported by the very outspoken perinephritis. However, the distinct cyst wall, though paper-thin with loose connective tissue on it, speaks against it. Perhaps we have to fall back on the alibi of some congenital malformation.

These three cysts were distinctly outside the renal parenchyma and appeared to have had no connection with it. In the second case there was, however, an intimate connection with the renal pelvis. Though the dissection of the cyst was done most carefully and without breaking it, the renal pelvis was opened. The opening itself was not seen, but much urine escaped from the renal pelvis into the wound.

All three patients were women, thirty-five, fifty-five, and sixty-five years of age. This corresponds with the general experience that most of such cysts are found in grown people, often in later years and more frequently in women.

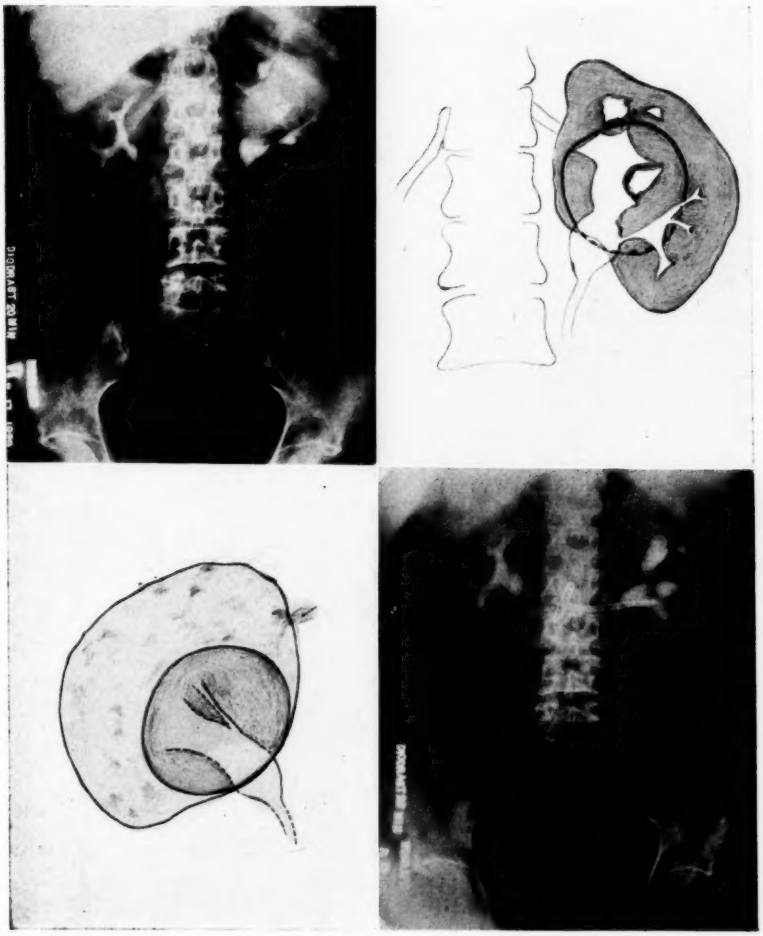

Fig. 3 (upper left) Case 3. Retrograde pyelogram. Evidence of pressure on the left renal pelvis. Note drawn out lower calices and absence of connection between lower part of pelvis and the peripapillary distal portion of upper calices.

Fig. 4 (upper right) Case 3. Outline of kidney and vertebræ traced through the x-ray film. Size and position of cyst shown by dotted line.

Fig. 5 (lower left) Case 3. Appearance of renal pelvis after opening the cyst. Note severe perinephritis, drawn out thin upper calix running entirely free through the cystic cavity. The main portion of the pelvis was almost completely free in the cyst cavity.

Fig. 6 (lower right) Case 3. Retrograde pyelogram taken twelve days after operation.

HISTORY OF MEDICINE IN WINONA COUNTY

(Continued from July issue)

Biographics

Samuel D. Miller was born in Union County, Indiana, about 1824. He served during the Mexican War, and came to Winona County in the fall of 1869. First he settled at Homer. He moved to Centerville in 1874, and four years later moved to Witoka. He was a member of the Legislature during the sessions of 1878-1879. He engaged in the drug business during his stay at Witoka. In 1882, he moved to the city of Winona, and died there from a dose of morphine in the year 1883. He was a member of the Masonic Order and of the Temple of Honor.

C. C. Moore, M.D., homeopathist and surgeon, came to Winona in 1856, giving many references on his card, three judges in Iowa, Wisconsin, and New York, a Wisconsin bank president, and Rev. H. S. Hamilton of Winona. The year following his establishment in Winona, he engaged in the jewelry business and continued in it for several years. During this time he probably continued to practice medicine.

William S. Morrison came to Winona County in the 1860's. In 1868 he moved from Lewiston to Fremont. There he continued to practice his profession for many years. In 1884 he opened an office at Lewiston, probably retaining his Fremont practice at the same time.

Edwin S. Muir came to Winona in 1898 from Plainview where he had practiced for four years following his graduation from the University of Minnesota in 1894. He was associated with Dr. W. T. English when he first came to Winona and succeeded Dr. English when the latter died. Dr. Muir was highly esteemed both by his professional confreres and the people of Winona. He served as Mayor of Winona for two terms. Dr. Muir remained in Winona until the time of his death July 14, 1919.

L. H. Munger graduated from the Missouri Medical College in 1879. He came to Saint Charles to practice in 1881. He may have moved to Stearns County for a time, but later he returned and became a member of the Winona County Medical Society.

William Netter, a doctor from Rochester, moved to Winona about April of the year 1882. William Netter was engaged in the drug business in Winona with Dr. Wedel during the sixties.

William J. Newberry, M.R.C.S., a practicing physician at Minnesota City, came in 1882 from London, England, and bought the residence and office of Dr. Walrath. Dr. Newberry was a licentiate of the Society of Apothecaries,

London. After coming to Winona County, he became a member of the Winona County Medical Society.

John C. Norton, A.M., M.D., settled at Homer in 1855. In that year he ran for the office of assessor. In January, 1857, the following card was published in the Winona paper:

J. C. NORTON, A.M., M.D.
Physician and Surgeon
Justice of the Peace
Land Surveyor, & Coroner
Homer, M.T.

Dr. Norton wrote a series of articles on the botany of Winona County which were published in the Winona paper in 1858. He was also a very popular lecturer.

Jean O'Hara, a homeopathic physician and surgeon, came to Winona about 1873. He was a druggist and physician between 1878-1885. Dr. O'Hara was a man of unruly disposition, and got into several small disputes during his stay in Winona. In 1884, he shot a barkeeper in the leg while drunk. At another time he had a man arrested and fined for shoving him off the sidewalk.

Dr. Palmer owned a farm in Winona County about 1882.

W. Thorton Parker graduated from the Royal University of Munich. He was surgeon of the White Earth Reservation before coming to Winona, and had been for a time a resident of Boston, Massachusetts. He located in Winona in May, 1881.

J. S. Pashley, M.D., physician and surgeon, settled in Winona with a view to permanent residence in July, 1865, and solicited a share of public patronage by his card in the newspaper.

D. C. Patterson, M.D., came to Winona in May, 1856, at which time the following card was published:

D. C. PATTERSON, M.D.
Late of Cleveland, Ohio
Will give his attention exclusively to the practice of
Medicine & Surgery

In 1859 Dr. Patterson took Dr. C. B. Dayton as a partner. Three years later, Dr. Patterson had left Winona, probably going directly to Washington, D. C., where he resided in 1879 and later.

E. H. Patterson was a Winona physician about 1860. Possibly confused with Dr. D. C. Patterson.

Dr. Peake practiced in Winona County about 1863.

J. L. Peregrine practiced in Winona about 1883.

Thomas A. Pierce, M.D., came to Winona from Galena in November 1863. At that time he published the following card:

THOMAS A. PIERCE, M.D.
Homeopathic Physician and Surgeon
Office over Wickersham's drug store
Second Street
References: W. W. Huntington, P. M.; E. A. Small, J. A. Packard, Galena, Ill.; A. E. Small, M.D., D. S. Smith, M.D., Chicago.

Dr. Pierce graduated in 1850 from the Homeopathic Medical College of Pennsylvania. Not long after coming to Winona to practice he took Dr. William A. Whippy as a partner. Dr. Pierce was much interested in politics and in educational matters. He served on the Board of Education in 1874 and in 1879. He was a director of the Board in 1880 and again in 1882. Dr. Pierce was known as the leading homeopathic practitioner of Winona for many years.

Charles H. Prague (or Pague), **M.D.**, was a graduate of the Bellevue Hospital Medical College of New York City, and a member of the Oneida Medical Society there. He came to Winona to practice in September, 1866, and remained there for a decade or more.

J. E. Putnam was listed as a Winona County physician in 1865.

August Putsch graduated from the Homeopathic Medical College of Missouri in 1869. In 1872 he practiced as a physician and surgeon in Winona. During 1872-1873 and possibly later, he had a jewelry store in Saint Charles. He still practiced in Winona in 1885.

Dr. Reddington was listed as a Winona County physician in 1864.

L. Redmon opened an office and started practice in Winona in May, 1882. Dr. Redmon was an early settler of Preston and was well liked there, both personally and as a physician.

Dr. Reinholz was a physician at Lewiston in 1883.

A. D. Reynolds was a Winona County physician about 1863.

Edson Rhodes, M.D., graduated from the Rush Medical College in 1883. He came to Winona the following year and became the partner of Dr. D. H. Stewart. Before his arrival, Dr. Rhodes had held the position of resident physician of the Cook County Infirmary, Chicago. He became a member of the Minnesota State Medical Society in 1885, and was also a member of the Winona County Medical Society.

William H. H. Richardson, M.D., came to the United States in 1854. In 1856 he took out citizenship papers in Fillmore County, Vermont. He practiced for many years at Montpelier, Vermont, until his coming to Winona in the spring of 1867. Upon arriving, he formed a partnership in the practice of medicine and surgery with Dr. Franklin Staples. Dr. Richardson is recorded as a graduate from the Bellevue College, New York. He was a charter member of the Winona County Medical Society, and became a member of the State Medical Society in 1870. Dr. Richardson died of apoplexy on June 10, 1874, in Winona. He was known as a thoroughly educated and skilled physician.

S. D. Richardson was a physician in Winona County about 1863-1865.

W. H. Robbins was a practicing physician at Saint Charles about 1879. He was medical examiner for the Royal Arcanum Council of Saint Charles and a charter member.

T. W. Roberts graduated from the Homeopathic Medical College of Chicago in 1884. He had practiced in Winona County for many years previous to that date, having come as early as 1866.

Carl H. Roemer came to Winona to practice in 1876, or before. He departed in 1877 on the pretext of seeing a patient in La Crosse. He had married a widow with tempting property a few months previously, and made his disappearance after drawing $4,000 from the banks. He returned later, but after another attempt to abscond in 1878, was caught and brought back by the sheriff.

F. H. Rollins, M.D., practiced in Winona County about 1880. In 1930 he was still practicing at Saint Charles.

Augusta L. Rosenthal, M.D., located in Winona for the practice of medicine and surgery in July, 1884. In her card she offered special attention to diseases of women. In 1885 she was proposed for membership in the Winona County Medical Society, but was not accepted because of her sex. However, she became a member of the Minnesota State Medical Society later the same year.

R. N. Sackett, physician and surgeon, practiced in Winona County about 1869-1870.

J. W. Scott graduated from the medical department of the University of Wooster in 1880. In February, 1882, he came to Saint Charles from Ohio, and started practice. He became a member of the Winona County Medical Society in the year of his arrival. In 1885, he served on the local Board of Health, and the same year he attended the conference of state and local boards of health and sanitary councils for southeastern Minnesota.

J. B. Seaman was a Winona County physician who came before the close of 1856. He practiced medicine to some extent but later advertised himself as a "surgeon-dentist."

Samuel B. Sheardown was born in Catlin, Chemung County, New York, on October 7, 1826. He commenced his practice in the office of Dr. Winton of Watkins, New York. He married Dr. Winton's daughter, Mary, and brought her to Winona in 1856. His card, published in January of that year, read as follows:

DR. S. B. SHEARDOWN
Physician and Surgeon

Having had long and extensive experience in both the above professions, offers his services to the citizens of Winona and the public at large. He will be found at any time, when not engaged, during the day and night, at his office in the Drug Store, opposite the Post Office.

In May of the same year, Drs. Sheardown and Cole formed a partnership. During the Civil War, Dr. Sheardown served as surgeon of the 10th regiment and was stationed for some weeks in hospital service at St. Louis, Missouri. He practiced in Winona, then at Stockton for several years before his departure, and was again at Stockton after the war. There he opened a drug store, and at the same time continued his medical practice. He was very much interested in the development of the village and in its

religious and educational growth. He owned a half interest in a very productive flour mill and also part interest in a creamery.

At the same time the political affairs of the country claimed his interest. He was an active Republican and was elected to the lower House of the Legislature in 1862 and to the Senate in 1869, and again to the House in 1881.

He went to the aid of the New Ulm people during the Indian outbreak in 1862-1863, and was present at the hanging of the thirty-eight Indians at Mankato, and acted as one of the examining surgeons, pronouncing life extinct.

Dr. Sheardown was one of the charter members of the Winona County Medical Society organized in 1869, and was its first president. He served again in that capacity in 1870, in 1877, and in 1889. He was also a member of the State Medical Society and held the office of treasurer from 1869 until the time of his death. In 1875-1876 he taught in the Winona Preparatory Medical School.

At several times Dr. Sheardown had an office in Winona and made the first attempt at establishing a hospital there. His practice at Stockton was large, however, and required most of his attention. In the year 1882, Dr. Sheardown was postmaster at Stockton.

In the year 1884 Dr. Sheardown and his son, Dr. T. W. Sheardown, opened an office in Winona and both remained there for a time. Dr. Samuel Sheardown died August 1, 1889.

Thomas W. Sheardown, M.D., was the son of Dr. S. B. Sheardown. He was born in 1856, the year of his father's arrival in Winona. In March, 1879, he graduated from the Jefferson Medical College in Philadelphia, after a two years' course, with high standing in his class. First he took up his practice at Lake Benton. In the year he started practice he became a member of the Minnesota State Medical Society. The following year, there was a note published in the Winona newspaper to the effect that Drs. Andrews and Groesbeck of Lake Benton complimented Dr. Thomas Sheardown on a successful amputation.

In 1881, Dr. Sheardown practiced in Stillwater, but in December of that year he moved to Minneapolis, where he opened a drug store. In November, 1883, he moved to Knoxville, Tennessee, to practice. It was the following year that he and his father opened an office in Winona. Some time later, he went to Chicago, where he did not practice medicine but was employed by the McIntosh Battery and Optical Company as manager of the stereopticon department. He remained with this company until his death in 1896.

Charles S. Sheldon came to Winona to practice in September, 1868. His card stated that he was a late resident physician of the Buffalo General Hospital. He had graduated from the New York College of Physicians and Surgeons in 1868. Dr. Sheldon was a charter member of the Winona County Medical Society and became a member of the Minnesota State Medical Society in 1871. While in Winona he was assistant superintendent of the Congregational Sunday School, and upon his departure from the city in December, 1871, he was presented with a watch chain and cross by that organization. He moved to Greenville, Michigan, after leaving Winona.

George Sieler was a practicing physician at Alma during the eighties or before. He became a member of the Winona County Medical Society.

Thomas M. Sime, physician and surgeon, came to Winona to practice in 1866. He was an oculist and aurist. During his stay in Winona he was involved in two court cases. In February, 1873, he brought suit against E. L. Frary to recover $40 for medical services in treating a sore eye. The case resulted in his being allowed $10 by the court. In 1874 a case was brought against him and he introduced Drs. D. A. Stewart and J. B. McGaughey, both men of high reputation, for the defense. In November of that year he sold out his interests in Winona and moved to Menomonie, Wisconsin.

A. O. Slade was a druggist and physician in Winona. He came about 1879 and lived there during the eighties. He was "Surgeon-at-Arms" for the Winona Archery Club.

Columbus G. Slagle was a physician and surgeon of Saint Charles. He was a charter member of the Winona County Medical Society, organized in 1869. During that year and the next he was the partner of Dr. Sudduth. After leaving Saint Charles he practiced in Minneapolis for many years.

M. K. Smart was listed as a Winona County physician about 1864.

J. G. Smith came to Winona and started practice in May, 1879. He had been the house surgeon and physician at Bellevue and Blackwell's Island Hospitals, New York City.

(To be continued in the September issue)

President's Letter

WITH all Europe a battleground, Japan trying to conquer China and threatening to involve most of Asia, and Italy fighting the British in North Africa, it is time the United States started better defense measures and embarked on a program for enlarging her army and navy. During the World War about 63,000 physicians volunteered and served as medical officers. At the June meeting of the American Medical Association in New York a resolution was passed by the House of Delegates offering the full services of the American Medical Association and of the physicians of our country as needed. Dr. George C. Dunham of the United States Army presented a plan for the procurement of professional personnel for the Medical Corp of the Army in the event of a national emergency. This will be worked out through the office of the American Medical Association.

Our State Medical Association has had a Committee on Military Affairs for many years and the procurement plan in our state will be worked out with the aid of this committee working in conjunction with the Council of our State Medical Association. A questionnaire has been sent to every physician inquiring whether he wishes to enlist for active service or home service, age, family obligations, and special qualifications, training, and experience. Each physician is expected to fill out the questionnaire and return it so a complete list of the physicians and their qualifications and answers will be on file in Chicago. Should there be a call of physicians the quota for each state will be determined and our State Committee on Military Affairs will designate the men needed to fill the quota in the State.

Selections will be based on many considerations with special attention to the responsibilities of the individual to family and community. When the questionnaire arrives, each physician is requested to fill it out and return as promptly as possible. While we all realize that a war would be a calamity and earnestly hope it will be averted, should it come, we as a body of physicians have a patriotic duty to fulfill. The same loyalty and self-sacrificing devotion which the physicians have shown in every emergency in our country's history is expected, and will, undoubtedly be shown again should the necessity arise.

B. S. Adams, President
Minnesota State Medical Association

EDITORIAL

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BUSINESS MANAGER
J. R. BRUCE

Volume 23 AUGUST, 1940 Number 8

MALARIA THREAT IN MINNESOTA

THE report of a survey by Daggy and others which appears in this issue of MINNESOTA MEDICINE shows a marked predominance of the anopheles mosquitoes in the valley of the Mississippi River in Minnesota. In view of the limited number of anopheles found in previous more limited surveys in Minnesota, it seems this constitutes a change in the species of mosquitoes in this territory.

Malaria has never been a serious problem, or any problem at all, in Minnesota. Two or three indigenous cases have been reported each year until 1939, when the number suddenly jumped to seventeen definite indigenous cases, and possibly four more of the total twenty-three cases reported in the state. Wisconsin has had a similar experience.

The situation has caused some concern in public health quarters. Attempts have been made to explain the apparent influx of malaria-carrying mosquitoes. The question has been raised whether damming of the Mississippi has provided more quiet and clean waters which this particular species prefers.

With an apparent abundance of malaria-spreading mosquitoes in the state all that is needed is a few accessible malaria patients for the disease to spread.

The influx into Minnesota of thousands of soldiers from the South for military maneuvers, which has already begun, will doubtless provide cases of smouldering malaria for the anopheles to work on. The anopheles exist in the regions where some forty or fifty thousand recruits will be encamped. It is safe to assume that the mosquitoes will have considerable access to the recruits.

The report calls attention to the increase in malaria in Minnesota last year and suggests the likelihood of a further increase this year. The profession should be malaria minded.

RUDOLPH MATAS: NESTOR OF AMERICAN SURGERY

IN LEGENDARY lore Nestor, King of Phylos in Ancient Greece, was the oldest and most experienced warrior who took part in the siege of Troy. His name has therefore come to be used as a title of honor and respect for those of advanced years who have reached leadership in any field of human endeavor. Very fittingly can it be applied to the case of Rudolph Matas, whose eightieth birthday occurs on September 12, 1940. His career as a surgeon, coupled with his work as a teacher and writer, entitles him to the highest degree of recognition and an enduring place in the topmost ranks of his fellows.

Matas received his medical degree in 1880 at the age of twenty, after the customary short novitiate of that period when medical knowledge was scanty. Supplementary training like fellowships was unknown and even internships were

rare and primitive, never obligatory. But Matas was quick to grasp opportunity and soon secured a demonstratorship of anatomy which he held for ten years and today regards it among the most profitable and happy experiences of his life. At thirty-four he became professor of surgery at Tulane and thereafter his record is one of steady progress and accomplishment.

While best known for his original and extensive work in blood vessel surgery, which revolutionized all the old ideas, Matas was a pioneer in many other fields of general surgery and made enduring contributions. His bibliography includes over four hundred titles covering practically the whole field of surgery. He devised many original procedures, especially for the relief of postoperative complications, which have later been rediscovered and publicized by others. For further details of these and other similar matters attention is invited to the current issue of the *Bulletin of the American College of Surgeons* which contains the addresses delivered at the testimonial dinner tendered to Dr. Matas in New Orleans earlier in the year, on the occasion of his completion of sixty years' practice.

To study the record of a life of achievement like that of Rudolph Matas is a refreshing interlude at a time like this when the world is filled with the echoes of the forces of destruction and the finer things of life are in the shadows.

—Gilbert Cottam, M.D.

QUARTERLY JOURNAL OF STUDIES ON ALCOHOL

THE appearance in June of the first number of the *Quarterly Journal of Studies in Alcohol* question why such a journal was not published in this country before. With the discontinuance of the *British Journal of Inebriety*, this new journal is the only one devoted to problems of alcohol published in English.

There is need for such a journal. The subject of alcohol is an important one and a journal devoted to it makes available authoritative and unbiased information on the subject. Information put out by the liquor interests or by the temperance league is questionable because of its source.

That this new journal will be scientific and reliable is assured by the personnel of the editorial board and the editor, Howard W. Haggard. The Research Council on Problems of Alcohol recently formed by the American Association for the Advancement of Science has chosen the journal as its official organ.

If the quality of the articles which appear in the first number of the journal is maintained in future issues the new publication will make a contribution to the problem of alcohol. Our best wishes for a long and useful mission are extended to the *Quarterly Journal of Studies on Alcohol.*

The journal is published at 4 Hillhouse Avenue, New Haven, Connecticut. Subscription price $3.00.

MINNESOTA EMPLOYMENT SERVICE

Every doctor knows the difficulties he faces when he finds it necessary to hire a new office girl, typist, stenographer, a laboratory technician or a registered nurse. Most of the trouble and annoyance usually encountered at such times can be avoided if the assistance of the employment service of the Division of Employment and Security is requested.

This governmental activity in Minnesota is under the direction of Victor Christgau. In pointing out that the service is free and is available to both employers and workers, Mr. Christgau says, significantly: "It's paid for. It should be used more!"

Under Mr. Christgau's administration, the service is being developed into an agency that serves the small employer in very much the same way as does the personnel department that all large business organizations find it so necessary to maintain.

The Minnesota Employment Service is a state-wide clearing house for workers and jobs—an organization that brings qualified people who seek employment to employers who have positions they want filled. Neither profit nor charity enters into its operations. It maintains the largest reservoir of employables in the state. Its records constitute a great pool of employee possibilities, a detailed examination of the more than 150,000 in approximately 3,000 different occupational classifications reveals.

When a doctor, for example, needs a new employee, all he has to do is to telephone detailed specifications to the nearest office of the state agency. There, trained placement officers search their files for workers who can meet these requirements. These placement officers are expert interviewers, men and women who have been specially trained and who know the qualifications that a given job requires. From their files they will refer one, two, three—or as many persons as the employer may desire to interview personally. From these referrals, the employer makes his own selection. In this way, he acquires a trained worker and loses no time interviewing a crowd of applicants. His time is not taken up by misfits.

The service of the Division of Employment and Security is state-wide and all its thirty-seven full time local offices can be reached by telephone.

MEDICAL ECONOMICS

Edited by the Committee on Medical Economics
of the
Minnesota State Medical Association
W. F. Braasch, M.D., Chairman

PREPARATION FOR MEDICAL DEFENSE

The first line of defense in modern warfare is medical defense and, unless this is adequately organized, success is impossible. The Council on National Defense is well aware of this and, as a first step in preparedness, requested that medical organization proceed at once. Although certain federal authorities, coöperating with politicians and a group of welfare workers, have made every effort in recent years to belittle the medical profession and besmirch organized medicine, with the threat of national danger they have been silenced and now hasten to acknowledge the profession's importance to public welfare. It should be stated, however, that the attitude of the Army and Navy has always been friendly and coöperative with the medical profession.

Important Issue

The most important issue before the medical profession today in any case is preparation for the national defense.

Physicians of America have never waited to be drafted for a national emergency. They have been ready and waiting whenever the need arose.

Today it is not a question of rushing out to enlist with the fighting forces. It is not a question of repairing the injuries of war. Instead, it is a question of organizing for a vital part in the preparedness effort of a nation.

Never again in America, it is to be hoped, will an actual declaration of war find a feeble fighting force bereft of equipment, and without the organized services of physicians ready at hand to judge the physical fitness of troops and workers, to rehabilitate the unfit and to care adequately for civilian needs at the same time that the overwhelming needs of the war injured are cared for.

To Provide Machinery

It is to provide the information and machinery for preparedness, not for war, that the new mobilization plan for physicians is now getting underway. The questionnaire sent out in July by the National Medical Preparedness Committee appointed by the American Medical Association in New York is the first step in that mobilization.

The National Research Council is also organizing representatives of the various fields of medicine so as to have available the most modern developments in medical progress. Plans are being made to set up schools of instruction in various fields, in order that those who are engaged in medical defense may be adequately instructed. Publication of a bulletin is being considered which will make information concerning recent developments immediately available.

This time the doctors of America are setting up their own organization for national defense as scientifically as they habitually set up their service for the care of the sick and the injured.

No Hit-and-Miss Enlistment

There is to be definite and detailed information about every physician on file in Chicago. Those who are likely to volunteer for war service, in case a war is declared, will be sent as they are needed to the places they are best qualified to fill. Those who will not for many reasons be assigned to fighting units will be marshalled at home according to the equally important need for proper selection of soldiers, for repair of correctible defects, for medical supervision of industrial workers and for uninterrupted service to the civilian population at home.

This time there will be no hit-and-miss enlistment of medical aid for the nation's defense forces and the questionnaire is the absolute essential guarantee of the new order.

Minnesota physicians have now received their questionnaires. Most of them have already sent them back carefully filled out to Chicago headquarters.

Reminder

A few still remain to be filed, however, and it is for the sake of the laggards, principally, that the post card plea of Dr. F. L. Smith of Rochester, State Chairman for the Committee on Medical Preparedness, went out to all members of the Minnesota State Medical Association this week.

The post card asked each member who had completed and mailed his questionnaire to notify the State Office on an attached card.

Thus all would be reminded of their duty, and also the state chairman would have in his possession a list of the doctors of Minnesota who had filled in the questionnaire to aid him in coöperating with the national committee.

Many a physician whose loyalty and willingness to serve in any capacity is beyond question, still finds it easy to postpone small chores like the filling and mailing of this questionnaire.

It is to these men that the state chairman and officers of the Association address a special plea.

This, for the present, constitutes the full military duty of the average practicing physician and delay in complying will cast an undeserved reflection upon the patriotism and loyalty of the profession in Minnesota.

FOR NATIONAL COORDINATION

A ringing call for coördination of medical and public health services under a coördinator of medical and health preparedness for national defense was sounded in New York recently by Surgeon General Thomas Parran.

The need for such a coördinator in times of peace as well as in times of stress such as these, has long been clear to the doctors of the country. The considerations which have kept the health agencies of the Children's Bureau separate and independent of those under the Surgeon General of the Public Health Service and have tried to bestow upon still another quarter federal efforts to aid industrial health, have been compounded of politics, personalities and precedents inherited from an earlier and simpler time. This is the time to strike hard for unified cohesive federal health services under competent medical control.

At the same time, it is a time for watching closely that no standards of freedom, independence and scientific quality, be sacrificed in a frenzy to convert the medical services of the nation over night into a strong arm of national defense.

Dr. Parran's address as printed in the *Journal of the American Medical Association* should be read by every physician for its provocative review of the immediate problems to be faced by physicians in bringing America to an adequate state of preparedness. His remarks on the subject of coördination are reprinted here for especial emphasis on this problem of coordination and leadership in the United States.

Health, Military Problems Inseparable

Said Dr. Parran:

"In time of stress, the health problems of the military and civilian population are inseparable. At present they are the responsibility of many unrelated Federal agencies having the happiest personal good will toward one another, but with no more official authority or compulsion toward coördinated action than did an airplane factory and an automobile plant two months ago. Each of these agencies legally can perform only certain functions set up by law. None of them has a close, working integration with the organized medical and public health professions. The State Health Departments are as diverse as the forty-eight states. None of the official agencies have the benefits of a full working relationship with the great voluntary associations for health and welfare, in which doctors, dentists, nurses, engineers, in their technical capacity, work side by side with citizens to caulk up the leaks in the hull of our national manpower. None of the official agencies has the full aid and service which the public spirited foundations set up to promote health and welfare are able to give. . . .

"I Propose a Coördinator"

"Our defense plans, for the immediate emergency, are still young. There is much in the way of organization and coördination yet to come. But as a first step in meeting the vital needs of manpower preparedness, I propose that a coördinator of medical and health preparedness for national defense be appointed under the National Defense Council. There is much for him to do. He would work with and through the Surgeons General of the U. S. Army, the U. S. Navy, and the U. S. Public Health Service, other Federal agencies, and the national voluntary organizations concerned with the prevention, diagnosis, and treatment of disease.

"A first task is the need for listing and classifying professional and technical personnel in the country;

for planning and aiding, if and when necessary, the recruitment and mobilization of medical and health personnel. . . .

"If or when war comes, every 1,000,000 men mobilized need 7,500 doctors drawn from civil practice. Dentists, nurses, sanitary engineers are needed too. In the mobilization of four million during the last war, more than a fourth of the effective medical men of the country were called to the colors. Whole counties were depleted of doctors. Many medical schools were almost put out of business, because the best men left for military duty. We should not repeat these mistakes. Today we should investigate who should go, who should stay to practice, to teach, to operate an essential civilian service. We have no machinery now to do this. A Coördinator of medical and health preparedness should create the machinery, working with the public health agencies, the schools, and the medical profession itself.

Malnutrition Cited

"If our workers are malnourished, they cannot be efficient in producing what we need for defense. Yet every survey of nutrition, by whatever method conducted, shows that malnutrition in this country is widespread and serious. For example, studies by the Department of Agriculture show that forty per cent of the people are not getting a diet adequate to maintain good health and vigor. Eight out of every ten in this category do not have an income sufficient to purchase, at market prices, a diet adequate in amount and kind; this in spite of the fact that the foods of which the Nation has an apparent surplus are those in which the dietary of so many is deficient—milk and milk products, citrus fruits, green vegetables, and meat.

"Not through any pity for their working people, but because their scientists proved to them it was an essential to national power, the Germans began several years ago to provide for the working masses a diet better than ours have now. We have made a beginning in this direction through the foodstamp plan. What we need is an intensive national drive, with rigid scientific controls, to use the food we have to improve the fitness of our manpower.

"There is no time for dogged adherence to outworn patterns, nor for a major change in proved forms of medical practice. Medical science grows, expands, opens up new possibilities for saving life and building strength. In the application of its basic sciences, medical practice must expand also to meet the new demands of the Nation for self-preservation."

"THREE YEARS COULD BE SAVED"

It is interesting at this time to recall that many efforts were made to modify or lower standards of licensure and medical graduation after the United States entered World War I.

The matter was discussed according to the July *Bulletin of the Federation of State Medical Boards of the United States*, at Federation meetings in February, 1917, and again at the annual session in 1918.

One board member declared that it was the obligation of the medical boards to protect and help humanity rather than look entirely to the preferment of doctors and that medical boards should be "reasonable and considerate to meet the needs of the times."

It was proposed that three years could be saved in preparatory education and another year could be eliminated from the medical course if men were taught only the things which are really essential to the making of a good general practitioner. The author further urged that "this great medical protectorate of federated medical boards assume the responsibility of establishing a new order of things" and create a committee forthwith with power to act.

"When it is made reasonably easy for men to become real doctors," the author declared in a quotation that should be of particular interest to medical educators today, "they will cease being cultists, and if we, as medical boards, are really trying to help humanity, this will aid us in the accomplishment of our duty."

Standards to Be Upheld

Fortunately, these proposals were vigorously opposed by other members of the federation.

In the event of another national emergency, the *Bulletin* declares, the Federation will again take a firm stand in upholding the highest standards of medical training required for efficiency in civil and military medical practice.

"PUBLIC LIABILITY INSURANCE"

(Monthly Editorial Prepared by the Medical Advisory Committee)

Recently, two cases brought to the attention of your medical Advisory Committee have made the discussion of the relationship between Physicians' and Surgeons' Liability (Malpractice) Insurance and Owners', Landlords' and Tenants' Public Liability Insurance pertinent.

In both cases injury followed closely on surgical treatment and loose interpretation of the points involved may place the defense within the wording of either or both of the policies carried.

The usual Malpractice Policy provides defense

for the Insured in event of legal procedure and indemnity for loss or expense resulting from claims for damages on account of malpractice, error or mistake committed or alleged to have been committed by the Insured in the practice of his profession, while the Owners', Landlords' and Tenants' liability policy indemnifies the insured against loss resulting from legal liability due to accidental injuries suffered by persons other than employes in the insured premises due to "ownership, care, maintenance or use" of the office quarters, including accidents involved in making ordinary repairs. This insurance would cover loss not included in the Physicians' Liability policy which provides only for losses due to the practice of his profession.

It is the thought of your Committee that it might be well for members of our Association to carry both. The cost would be little additional. The security and peace of mind warrants the small outlay. The defense, of course, would have fewer complications and would be facilitated generally if both policies were carried in the same indemnifying company.

—B.J.B.

MINNESOTA STATE BOARD OF MEDICAL EXAMINERS

Julian F. Dubois, M.D., Secretary

Supreme Court of Minnesota Upholds Mower County District Court in Denying Austin Physician and Fraternal Order of Eagles an Injunction against the Minnesota State Board of Medical Examiners

Re: Fisch, et al. vs. Sivertsen, et al.

On June 21, 1940, the Supreme Court of Minnesota in a unanimous opinion, sustained the District Court of Mower County in dismissing the lawsuit instituted by Dr. Herbert Matthew Fisch, a physician and surgeon of Austin, Minnesota, and Lookout Aerie No. 703, Fraternal Order of Eagles, against the Minnesota State Board of Medical Examiners.

The Honorable Norman E. Peterson, Judge of the District Court for Mower County, had made an order on October 21, 1939, dismissing the plaintiffs' lawsuit, and on December 21, 1939, Judge Peterson made a further order denying the plaintiffs a new trial; it was from this order that the plaintiffs appealed to the Supreme Court of Minnesota.

The plaintiffs instituted the lawsuit in July, 1939, following an informal hearing held by the Minnesota State Board of Medical Examiners, and after a ruling by the Honorable J. A. A. Burnquist, Attorney General of the State of Minnesota, and Mr. John A. Weeks, Assistant Attorney General, that the Fraternal Order of Eagles and Dr. Fisch were violating the laws of the State of Minnesota, and particularly those relating to the practice of healing and the practice of medicine. The Attorney General also ruled that any physician who was a party to the operation of such a plan, subjected himself to the possible loss of his license as a physician. The legal objection to the operation of such a plan is that the Fraternal Order of Eagles, a corporate entity, acts in the capacity of an intermediary in the practice of medicine contrary to law and usurps the privilege and franchise of the practice of medicine, in violation of law. The plaintiffs attempted, in their lawsuit, to enjoin the Minnesota State Board of Medical Examiners from interfering with the plan and also from taking any action to suspend or revoke Dr. Fisch's license as a physician. As originally instituted, the lawsuit was also brought against the members of the Mower County Medical Society, but the plaintiffs voluntarily dismissed their case against those defendants when the case was called in Court.

As operated, the Fraternal Order of Eagles at Austin, charged its members $12.50 per year dues, and out of this amount the sum of $4.00 per year per member was allocated for medical care, the money being divided equally between Dr. Fisch, a physician and surgeon, and Dr. Nicholsen, an osteopath.

Following the Supreme Court's decision and under date of July 15, 1940, Dr. Fisch notified the Minnesota State Board of Medical Examiners that he had resigned as Aerie Physician at Austin.

License of Hastings Physician Suspended for Three Years in the Matter of the Revocation of the License of Norbert J. Kulzer, M.D.

On July 12, 1940, the Minnesota State Board of Medical Examiners, following a hearing, suspended for three years the license to practice medicine held by Norbert J. Kulzer, M.D., of Hastings, Minnesota. The Medical Board found Dr. Kulzer guilty of immoral, dishonorable and unprofessional conduct as defined by law. The complaint against Dr. Kulzer grew out of Dr. Kulzer's alleged misconduct with a woman patient. Dr. Kulzer frankly admitted his guilt, but pleaded extenuating circumstances, and begged for leniency.

Dr. Kulzer was born at Melrose, Minnesota, in 1905, and graduated from the Medical School of the University of Minnesota in 1933. He was licensed in Minnesota by examination in 1934.

STATE LABORATORY FACILITIES

The Division of Preventable Diseases of the Minnesota Department of Health is open Saturday mornings for routine examinations. Specimens considered to be emergencies by the physicians submitting them will be examined Saturdays or Sundays on special request. Due to a misunderstanding, physicians have been under the impression that these laboratories operate on a five-day week. This is not true, since the laboratories are open 365 days in the year.

To serve physicians who occasionally must have specimens examined immediately, service is available in the morning on Saturdays, Sundays and holidays, and a twenty-four-hour service is maintained for pneumococcus typing. Although the Division of Preventable Diseases requests that emergency work be kept at a minimum, its facilities are available seven days each week.

MINNESOTA DEPARTMENT OF HEALTH
A. J. Chesley, M.D.
Secretary and Executive Officer

OF GENERAL INTEREST

A practice has been established in Badger by Dr. Herman J. Holte, formerly of Seattle, Washington.

* * *

Dr. E. L. Baker of Minneapolis rounded out thirty years of practice in Minneapolis, July 15.

* * *

A new hospital building was recently opened in Tracy under the guidance of Dr. W. H. Valentine.

* * *

Dr. and Mrs. Walter H. Ude of Minneapolis spent a month's vacation in Alaska and the Canadian Rockies. They left Minneapolis, June 22.

* * *

Dr. Meyer Z. Goldner has opened offices at 1129 Medical Arts Building, Minneapolis, for the practice of orthopedic surgery.

* * *

Dr. Milo H. Larson, of Norwood and Cologne, has returned to Nicollet, repurchasing his practice and the Nicollet Hospital.

* * *

Drs. John A. C. Leland, Jr., and Frederic F. Wipperman have been commissioned Lieutenants (junior grade) in the Medical Corps, U. S. Naval Reserve.

* * *

Dr. N. F. Musachio, who has been associated in practice with Dr. Clarence Henry of Milaca for the past year, will locate soon in Foley, it is announced.

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Dr. A. E. Osterberg of Rochester attended a meeting of the Committee on Chemical Service to Medicine of the American Chemical Society in Ithaca, New York, June 28.

* * *

Reclassification of employees of the Minnesota State Department of Health under the new civil service act is under way, and adjustments are now being made in the department.

* * *

Dr. and Mrs. W. B. Dublin of Rochester have gone to Fort Steilacoom, Washington, near Tacoma, where Dr. Dublin has become associated with the Western State Hospital as pathologist.

* * *

To become associated with the Lemley Clinic at Rapid City, South Dakota, Dr. R. S. Ahrens has resigned as assistant superintendent of the Fergus Falls State Hospital.

* * *

After practicing medicine in Nicollet village since April, 1939, Dr. C. F. Wohlrabe has moved to North Mankato where he has opened an office at 300½ Belgrade Avenue.

* * *

Dr. R. K. Dixon of Denver, formerly of Rochester and St. Charles, flew to Minnesota to participate in dedicatory exercises of Crystal Springs trout ponds near St. Charles, June 29.

Dr. William A. O'Brien of Minneapolis will give the banquet address at the meeting of the American Hospital Association in Boston, September 19. His topic will be "An Education Program for Hospital Administrators."

* * *

Dr. C. L. Warren of Chicago, a former Minnesota physician, passed away June 25 in Chicago. His wife and four children, Eugene, Clark, Florence and Chester, survive. Dr. Warren practiced at LeRoy and at Brewster.

* * *

Dr. Robert S. Hunt, a graduate of Northwestern University Medical School, has located at Fairmont where he is associated with Dr. R. C. Hunt in the Hunt Hospital. He interned at St. Mary's hospital in Minneapolis and at the Cook County Hospital, Chicago.

* * *

Dr. Hugh R. Butt of Rochester addressed a meeting of the American Association for the Advancement of Science, research conference on the subject of vitamins, at Gibson Island, Baltimore, July 19. His subject was "Clinical Studies of Vitamin K Deficiencies."

* * *

Winners of Hospital Day awards, as announced by the Council on Public Education are: large hospital class, the Nopeming Sanatorium of which Dr. A. T. Laird is the director; small hospital field, the Glenwood Hospital, of which Dina Bremness is the superintendent.

* * *

Dr. S. Marx White of Minneapolis has been elected to the Hennepin County Sanitarium commission. He succeeds Dr. F. E. Harrington. Dr. White previously served on the commission for eighteen years, from 1919 to 1937.

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Dr. J. A. O'Hanlon has opened an office in Norwood, Minnesota. A graduate of the Marquette University Medical School at Milwaukee, he has been associated with the Webber Clinic in Duluth for the past four years.

* * *

New Diplomates of the American Board of Obstetrics and Gynecology through qualifying in the June examination held in Atlantic City are Drs. Charles Hugh McKenzie, Owen Francis Robbins and William Paul Sadler of Minneapolis.

* * *

Dr. Rollin E. Cutts, until recently of Minneapolis, is associated with the department of child hygiene in the Illinois State Department of Health at Springfield, Illinois. While practicing in Minneapolis, he was on the staff of the University of Minnesota Medical School, pediatrics department.

* * *

Dr. Morris Fishbein of Chicago, editor of the *Journal of the American Medical Association*, addressed members of the Mayo Clinic staff and Fellows of the Mayo Foundation, July 26, at the Mayo Foundation

House in Rochester. His topic was "Problems Involving Medical Preparedness."

* * *

Dr. L. C. Barr and Dr. D. L. Donovan have become associated in practice in Albert Lea, establishing offices at 306 Freeborn County National Bank Building on South Broadway. Drs. Barr and Donovan practiced with the late Dr. H. D. Burns of the past five years, though recently Dr. Barr had offices of his own.

* * *

Dr. John E. Low of Saint Paul has become associated in practice with Dr. J. J. Ederer at the Mahnomen Hospital in Mahnomen. Dr. Low, who received his M.D. degree from the University of Minnesota Medical School this year, interned at Ancker Hospital in Saint Paul.

* * *

Dr. H. M. Keith of Rochester was renamed president of the Minnesota Mental Hygiene Society at a meeting of the board in June. Other officers are Mrs. Stella Ames of Saint Paul, vice president; Miss Elizabeth Glynn of Minneapolis, secretarp; Stanley Hedstrom of Saint Paul, treasurer.

* * *

Dr. Theodore F. Hammermeister has resumed his practice of general medicine and surgery in New Ulm after a prolonged leave of absence. He is president of the Union Hospital Medical Surgical Staff and vice president of the Loretto Hospital Medical and Surgical Staff.

* * *

Three papers were presented by Dr. John S. Lundy of Rochester at a meeting of the Pacific Northwest Medical Association in Spokane, Washington, in July. The papers were: "Intravenous Anesthesia with Pentothal Sodium," "Choice of Anesthetic" and "Regional Anesthesia; Its Place in Present-day Anesthesia."

* * *

A new appointment to the University of Minnesota Medical School faculty is that of Dr. Lemen Jonathon Wells, who has been named associate professor of medicine. Dr. Wells held the posts of instructor of anatomy at the University of Missouri from 1935-37, and of assistant professor of anatomy since 1938.

* * *

The Minnesota State Department of Health has set up division headquarters at Little Falls to supervise sanitary engineering and public health aspects, as 50,000 men mobilize during July and August in the largest troop mobilization ever to be conducted in the state. Directing operations are Dr. Ralph R. Sullivan and Harold A. Whittaker.

* * *

Dr. and Mrs. Robert N. Bowers, who were married March 9, are making their home in Mazeppa, where Dr. Bowers began practice on August 1, 1940. A graduate of the University of Minnesota Medical School, Dr. Bowers recently completed an interneship at Grand Hospital in Columbus, Ohio. Mrs. Bowers is the former Miss Lenna Guthrie of Columbus.

* * *

Dr. Ole Heiberg, a graduate of the University of Minnesota Medical School in 1935, has opened a practice in Montevideo. His offices are in the Security Bank Building. After graduating from the University, Dr. Heiberg was resident physician in the Minneapolis General Hospital for three years. For the past two years, he has been a member of a clinic in Manhattan, Kansas.

* * *

Dr. Carl W. Anderson, national champion of hurdlers in 1923-24 and now assistant medical director of the Northwest National Life Insurance Company of Minneapolis, was an official at the National inter-collegiate track meet staked at the University of Minnesota in June. He acted in the capacity of Judge of the finish. Dr. Anderson was the United States hurdler representative in the Olympic games in 1924.

* * *

Two Virginia, Minnesota, clinics will occupy offices on the second floor of a new building now being erected at Second Street South and Third Avenue in that city. The Malmstrom & Sarff Clinic, and the Morsman Eye, Ear, Nose and Throat Clinic expect to move into the building about September 1. About thirty rooms are being provided for offices and laboratories on the second floor.

* * *

Worthless checks have been passed recently in two Minnesota towns by a man who represented himself as a "Dr. Daly," looking for a location to open a practice. The checks were drawn on a Montevideo bank and came back marked "Unknown." Investigation reveals no person of that name in Montevideo. Physicians should be warned against similar attempts in other towns.

* * *

Dr. A. G. Sanderson has been elected president of the Riverside Sanatorium in Granite Falls. He fills the vacancy created by the death of Timothy O'Connor of Renville. Dr. G. H. Mesker of Olivia was chosen vice president. Members of the purchasing committee are Dr. H. A. Roust of Montevideo, B. A. Deterling of Granite Falls and Dr. Sanderson. Dr. L. S. Jordan is superintendent and medical director.

* * *

The practice of the late Dr. H. D. Burns of Albert Lea has been purchased by Dr. D. S. Branham, his former associate for ten years, and Dr. S. A. Whitson of Alden. They have taken over Dr. Burns' office in Albert Lea, and will also continue the Alden practice of Dr. Whitson who was located in that city for twelve years. Dr. Branham and Dr. Whitson have been associated in the practice of surgery for the last four years.

* * *

Dr. Harold S. Diehl, dean of medical sciences at the University of Minnesota, heads an all-university committee appointed to coördinate the university's efforts to coöperate in national defense efforts.

The defense efforts include: pushing two medical school research projects, one of which is concentrated on medical surgery and the other on human fatigue; organization of the United States General Hospital No. 26, comprising about forty medical officers; training men in the naval R.O.T.C.; participating in the civil aeronautics authority flight program; and the loaning of Dr. Elvin B. Stakman, internationally known plant

pathologist, to a federal expedition to South America to study possibility of expanding rubber production.

The university is one of four selected to assist in studies of the impact of the preparedness and defense program on business.

* * *

Equipped with the most modern facilities, two new neuro-surgical operating rooms have been opened at St. Mary's hospital in Rochester. They were built at a cost of more than $50,000. A feature of both rooms is a glass screen which separates the operating surgeon from surgeons and nurses who may be observing. Communication is possible by means of a sliding panel in the glass. An x-ray cabinet on the wall allows the operating surgeon to study x-rays of the patient while he is working. For the benefit of spectator surgeons, a moving picture of similar operations may be exhibited in the room as an operation is being performed.

* * *

Dr. J. C. Litzenberg, professor emeritus of the Department of Obstetrics and Gynecology at the University of Minnesota Medical School, was elected president of the American Gynecological Society at the organization's meeting in Quebec, June 17-19., Dr. Litzenberg was also re-elected to the American Board of Examiners of Obstetrics and Gynecology for a five-year term.

Dr. M. J. Shapiro of Minneapolis has been named a member of the American Heart Association committee for the study of rheumatic diseases, which will devote its time to setting up standards for the care of children with rheumatic fever. The committee will publish a pamphlet on this subject early next year under the editorship of a special committee, composed of Dr. Shapiro, Dr. Edward F. Bland of Boston and Dr. Helen Brooke Taussig of Johns Hopkins Hospital in Baltimore.

Dr. Shapiro presented a paper before the American Heart Association at its meeting in New York City in June.

* * *

Among the new names in the 1940-1941 edition of "Who's Who in America," are those of sixteen Minnesota physicians. In all, there were seventy-five Minnesotans included in the volume for the first time.

New from Minneapolis are the names of Drs. George Edmeston Fahr, Arthur Douglass Hirschfelder, John Leyland McKelvey and John Charnley McKinley.

Dr. Everett K. Geer is new in the Saint Paul list.

New on the Rochester list are the names of Drs. Arlie R. Barnes, David M. Berkman, Albert C. Broders, Fred W. Gaarde, Herbert Z. Giffin, Howard K. Gray, Norman M. Keith, Frank H. Krusen, Charles W. Mayo, Robert D. Mussey and Gordon B. New, all of the Mayo Clinic staff.

Among the most outstanding members of the "Who's Who" family who have died during the biennium and consequently are no longer recorded in the volume are Dr. Charles H. Mayo and Dr. William J. Mayo. Of the sketches in the previous edition, that of Dr. Charles H. Mayo was the longest. The new edition has 31,752 names, as compared with 8,600 in the initial volume published in 1899.

The University of Minnesota medical class of 1920 has taken over the first annual membership campaign for the Minnesota Medical Foundation, it is announced by Dr. Erling S. Platou, president.

The campaign will wind up with a scientific program and reunion to be held in connection with Homecoming on the University campus next fall. Meetings will be held in the new Minnesota Union.

Membership in the Foundation is increasing rapidly and is far beyond the expectations of those first interested in this foundation of medicine, which is for all alumni and friends of the University Medical School. The Foundation prints a bulletin containing scientific articles, which is sent to all members.

A great deal of interest in the Minnesota Medical Foundation was evidenced at the reunion of the Minnesota medical alumni held at the Madison Hotel in New York City during the meeting of the American Medical Association. Approximately fifty persons, including many residing in the East, attended the reunion, at which short informal talks were given by Dr. H. S. Diehl, Dr. Platou and Dr. Harold G. Benjamin, president of the Minnesota Alumni Association.

* * *

July 14 was "Ridgway Day" in Annandale, residents honoring Dr. Alfred M. Ridgway, who noted his fiftieth anniversary as a physician in that city.

Beginning practice in the "horse and buggy days," Dr. Ridgway has been the family friend, neighbor and dependable confidant of hundreds and hundreds of Annandale people in his fifty years of medical service in that community.

Regarding Annandale as a temporary location when he came there in 1890, Dr. Ridgway stayed on as his practice kept increasing each year. As "country doctor," Dr. Ridgway first used a two-wheel cart pulled by a single horse on his visits to patients through the countryside. Later, he had six horses (eight in the winter). His first motorized vehicle was a one-cylinder chain-drive Cleveland, which gave him wonderful mechanical experience.

For the past forty years, Dr. Ridgway has been a physician for the Soo Line railroad, being given that appointment following a train wreck near Maple Lake at which he gave passengers medical aid. He belongs to the Soo Surgical Society and the Interstate National Railroad Surgeons, as well as the Minnesota State and American Medical Associations. Dr. Ridgway helped to organize the Wright County Medical Society nearly fifty years ago.

Before studying medicine, Dr. Ridgway was a registered pharmacist in Minneapolis. To obtain funds to study medicine, he opened a real estate office in Minneapolis in January, 1886. Business was so good that in September he had enough money to enroll in the University of Minnesota Medical School. He interned at the Minneapolis General Hospital.

Since 1930, Dr. Ridgway has been assisted in his practice at Annandale by Dr. Lester H. Bendix, a graduate of the University of Minnesota Medical School in the class of 1930.

In Memoriam

Hiram D. Burns

Dr. Hiram D. Burns, for nearly twenty-five years one of the leading physicians of Albert Lea, died very suddenly June 19 while visiting his farm near his home.

Dr. Burns was born at Litchfield, Minnesota, March 20, 1889. He spent his boyhood in Minneapolis and at Omaha where he graduated from high school in 1908. He received his medical degree from the University of Nebraska Medical School in 1914. At medical school he was a member of the Phi Rho Sigma medical fraternity. His internship was served at the Clarkson Memorial Hospital of Omaha.

In 1915, Dr. Burns married Corinne Searle of Omaha and came to Albert Lea to practice.

Dr. Burns has shown an interest in community activities having been past-president of the Chamber of Commerce and the Rotary Club, a member of the Y.M.C.A. Board of Directors and the school board and a devoted worker in the First Presbyterian Church. He was a man of good judgment and of deep personal convictions in matters of civic affairs. He was not deterred by any type of opposition from giving able expression by word and action to his convictions. He was successful in his profession, a loyal friend—and will be greatly missed by this community, its hospital and entire staff. He was also a 32nd Degree Mason.

He was associated at first with the late Dr. R. G. Stevenson and later with Dr. Leo Donovan. He was a member of the Freeborn County Medical Society, the Minnesota State and American Medical Associations. At one time he served as president of his local medical society.

Dr. Burns' avocation was farming and he has built up some of the finest dairy herds in the country.

He is survived by his widow; a son, Robert Burns, and three daughters, Catherine, Alice and Marjorie. His mother, Mrs. Alice Burns, and a brother, Dr. Douglas Burns of Omaha, also survive.

—A. Gulixson, M.D.

Malvin M. Hauge

Dr. Malvin M. Hauge of Clarkfield, Minnesota, died at his home on January 31, 1940, of myasthenia gravis, aged sixty-three.

Dr. Hauge was born in Bremangerpollen, Norway, February 6, 1876. Left fatherless at the age of one year, he spent the early years of his life as a clerk and sailor, traveling in foreign waters extensively, until shortly before he came to this country in 1897. He came directly to Minneapolis where he started as a student at Augsburg Seminary. Dr. Hauge received his Master of Arts degree from Augsburg Seminary in 1902, and his Doctor of Medicine degree from Hamline University School of Medicine in 1907. In 1914, he took a postgraduate course in the postgraduate school of Medicine, University of Vienna, Vienna, Austria. In 1936, he became a member of the American College of Surgeons.

Dr. Hauge was married in Minneapolis, April 4, 1903, to Anna Schjelderup. He is survived by his wife and six children, Malvin, Cecelia, Waldemar, Erling, Bergliot, and Dagmar.

He began the practice of medicine in Clarkfield in 1907, continuing there until a few months before his death. In addition to carrying a large practice, Dr. Hauge was a leader in both civic and musical circles. He was a member of the Camp Release District Medical Society, the Minnesota State Medical Association, and the American College of Surgeons.

William D. Kelly

Dr. William D. Kelly was born in Saint Paul in 1864. He was the eldest son of Daniel and Mary Kelly, pioneer settlers of Saint Paul. He attended the parochial and public schools in Saint Paul, where he received his preliminary education. Later he entered the Philadelphia College of Pharmacy and after graduating from that institution he matriculated at Jefferson Medical College in Philadelphia, from which he received a degree in 1887.

Returning to Saint Paul he began the practice of medicine and was active in his profession until shortly before his death, which occurred in St. Joseph's Hospital, April 7, 1940. During the course of his medical career, Dr. Kelly served on the staff of both the Ancker and St. Joseph's Hospitals. He spent two years in the late nineties visiting the various surgical centers in continental Europe, and also visited clinics in Edinburgh and London.

He was a one time member of the American Medical Association, the Minnesota State Medical and the Ramsey County Medical Society. He was also an honorary member of the University of Minnesota chapter of Alpha Kappa Kappa fraternity. Dr. Kelly served for several years, beginning in 1904 with the rank of Major, in the hospital service of the Third Infantry of the State of Minnesota. For more than twenty years he was the medical representative of the Milwaukee Railroad in Saint Paul and also served as medical officer to the Federal Court of this district for many years. Dr. Kelly was an active member of the Junior Pioneers and the Knights of Columbus and a former member of the Benevolent Order of Elks.

MEDICAL BROADCAST FOR AUGUST

The Minnesota State Medical Association broadcasts weekly at 11:00 o'clock every Saturday morning over Station WCCO, Minneapolis, Station WLB, University of Minnesota, and KDAL, Duluth.

Speaker: William A. O'Brien, M.D., Professor of Preventive Medicine and Public Health, Medical School, University of Minnesota.

The program for the month will be as follows:

August 3—Leg Cramps
August 10—Hyperchlorhydria
August 17—Embolism
August 24—Sacro-iliac Disease
August 31—New Dentures

AMERICAN BOARD OF OPHTHALMOLOGY EXAMINATIONS

The Board will hold only one written examination in 1941 and this will be in March in various cities throughout the country. Applications should be made before December 1, 1940.

Oral examinations will be held in May and October and a special one on the Pacific Coast if candidates warrant.

Address American Board of Ophthalmology, 6830 Waterman Avenue, Saint Louis.

AMERICAN CONGRESS OF PHYSICAL THERAPY

The nineteenth annual scientific and clinical session of the American Congress of Physical Therapy will be held September 2 to 6, inclusive, at Hotel Statler, Cleveland, Ohio. This year there will be a departure from the usual arrangements in that the mornings will be devoted to an instructional seminar with the scientific program presented afternoons and evenings. This enables physicians to economize on time by attending both the instruction course and the annual convention during the same week.

Registrants may pursue only the individual courses they desire. The complete course consists of twelve lectures from a diversified list of forty-eight. The scientific program itself consists of papers, demonstrations and motion pictures covering every branch of physical therapy. There will be a separate scientific program covering eye, ear, nose and throat subjects. Write for schedule, fees, et cetera, to the American Congress of Physical Therapy, 30 North Michigan Avenue, Chicago, Illinois.

AMERICAN NEUROLOGICAL ASSOCIATION RESOLUTION

The American Neurological Association, in its Executive Session at the Westchester Country Club, Rye, New York, on June 7, 1940, unanimously passed the following resolution and directed its Secretary to send copies of this resolution to the Secretary of each State Board of Medical Examiners and to the editors of the *Journal of the A.M.A.* and of each State Medical Journal:

WHEREAS official statistics indicate that the immigration of refugee physicians is numerically small, representing in its totality less than 0.6 per cent of the practising physicians of this country;

AND WHEREAS such an influx of physicians from abroad cannot adversely affect the economic welfare of American physicians if the émigrés are distributed widely to those sections of the land in which they are needed;

AND WHEREAS information gathered from governmental and private investigations indicates that there are at least 2,000 communities in this land in need of immediate medical staffing which in large part cannot be supplied by the graduates of our own medical schools;

AND WHEREAS many of the demands for physicians come from states in which it has become impossible, either by reason of legal enactments or because of regulations of the State Boards, for the refugee physician to take his medical license examinations;

AND WHEREAS there now exists in New York a competent agency for diverting the unfit among the refugee physicians into non-medical fields thus making it possible only for those who are fit in training and in personality to be considered for examinations;

NOW THEREFORE BE IT RESOLVED that the State Boards of Medical Examiners in the United States shall create a uniform policy with regard to refugee physicians so as to make possible the wide distribution of these physicians to those places where they are needed throughout the land;

AND FURTHER that these uniform changes in the regulations of our State Boards shall be in the direction of the recommendations made by Dr. David L. Edsall in his article on "The Émigré Physician in American Medicine" (*Journal of the A.M.A.*, March 23, 1940, Volume 114, pages 1068-1073);

AND FINALLY that the Committee for Resettlement of Foreign Physicians of the National Refugee Service, Inc., 165 West 46th Street, New York City, shall be utilized as a clearing house for information in regard to available emigré physicians for specific placements.

—HENRY ALSOP RILEY, M.D., *Secretary*.

MISSISSIPPI VALLEY MEDICAL SOCIETY

The Sixth Annual Meeting of the Mississippi Valley Medical Society, "The Mid-West's Greatest Intensive Post-Graduate Assembly for General Practitioners," will be held at the Hotel Fort Armstrong, Rock Island, Illinois, September 25, 26, and 27, 1940. The program will be given by thirty-two clinician-teachers who will give over sixty lectures, demonstrations, round table discussions, et cetera. Further information may be secured from the Secretary, Harold Swanberg, M.D., W.C.U. Building, Quincy, Illinois.

Meeting of May 8, 1940

The regular monthly meeting of the Minnesota Academy of Medicine was held at the Town and Country Club on Wednesday evening, May 8, 1940. Dinner was served at 7 o'clock and the meeting was called to order at 8:10 p. m. by the president, Dr. James Johnson.

There were thirty-eight members and two guests present.

Minutes of the April meeting were read and approved.

The scientific program followed.

EOSINOPHILIC LEUKEMIA OR MYELOGENOUS LEUKEMIA WITH EOSINOPHILIC HYPERLEUKOCYTOSIS.

Case Report with Discussion of the Medical Literature

J. A. Lepak, M.D.
Saint Paul, Minnesota

Eosinophilic leukemia is a rare and much disputed disease. Only a few reports are found in the medical literature and some of those do not remain unchallenged. No doubt additional cases have been observed and studied but not recorded, because the very definition, description, and designation of what constitutes this condition varies so widely among scholars of hematology as to preclude a satisfactory discussion. The following case, typical or atypical as it may be, in accordance with the views expressed by the different hematologists, is, therefore, presented more to stimulate further discussion of the medical nature of this condition, rather than to add something new about it to our scientific knowledge.

Case Report

A man, single, aged forty-one, seeking relief for a backache, fever, abdominal distress, loss of weight, and severe pains in the hips and lower extremities, was admitted to St. Joseph's Hospital on December 1, 1939.

The past history revealed that in October, 1929, he had received treatment for a week in the hospital for chronic alcoholism, acute bronchitis, and nervous exhaustion. A month later a tonsillectomy had been performed. In 1930 he received treatment again for chronic alcoholism in the hospital for two weeks. During these hospital stays, however, he had no blood examinations. On November 30, 1937, he entered the hospital on Dr. E. K. Geer's service and remained there until March 21, 1938. Positive tubercle bacilli were found in the sputum and it became necessary to collapse the left lung. He also developed an ulcerative tuberculous infection involving the proximal half of the ascending colon, the cecum, and terminal ileum. Stool examinations showed no parasites. Sedimentation rates on two occasions were 8 and 12 mm. for one hour, respectively. During this hospitalization several blood examinations were made and revealed a persistent eosinophilia.

The air in the left chest was then replenished about once a month and he remained quite well until September 1, 1939, when he was attacked by an upper respiratory infection. Gradually he grew worse and on November 15, 1939, he was tired, listless, feverish, pale and complained of severe backache, enlargement of the abdomen, abdominal distress, severe pains in the hips and excruciating aches in the lower extremities. The examination now revealed, in addition to the previous findings an enlarged liver, a large tender spleen, and a fever of 100 degrees. A myelogenous leukemia existing concomitantly with the tuberculous processes was suspected and hospitalization was advised, but delayed until December 1, 1939, when the night sweats became severe, cough marked, fever 101 degrees, dyspnea pronounced, pain more severe in the left side of the abdomen and the patient semiconscious. On admission urinalysis showed a faint trace of albumin and many hyaline and granular casts. Blood examination showed: hemoglobin 82, red blood count 4,180,000, white blood count 40,300; polymorphonuclear 45 per cent, eosinophils 30 per cent, basophils 4 per cent, small lymphocytes 11 per cent, large lymphocytes 5 per cent, monocytes 5 per cent, metamyelocytes 1 per cent, myeloblasts, 4 per cent, myelocytes 6 per cent, band cells 6, non-S-shaped 7, multilobed 21, and the laboratory commented: "Summary of findings indicates a marked myeloid reaction, which probably represents a myelogenous leukemia, although the picture seems to be atypical. The eosinophilia and toxic changes have been seen in previous examinations and the above picture seems to be superimposed upon these findings." An X-ray picture of the abdomen confirmed the presence of a large spleen extending down to the level of the iliac crest. In spite of the usual supportive measures, on the second hospital day the patient became comatose and the temperature rose to 102.4 degrees, on the third day to 105 degrees, and on the fourth, just before death, to 106.8 degrees.

Due to the peculiar temperament of the family, it is to be regretted, no punctures nor special studies were

Blood Examinations

Date	12-1-37	12-22-37	2-2-38	2-5-38	3-12-38	9-15-39	12-1-39
Hemoglobin	102		94	94	94	86	82
Red Blood Cells	5,470,000		4,920,000	4,820,000	4,820,000	4,460,000	4,180,000
White Blood Cells	9,450	12,250	11,800	11,550	15,550	12,100	40,300
Polymorphonuclears	40	35	50	34	50	32	45
Eosinophiles	15	20	12	11	19	25	30
Basophiles	1	1	0	1	0	2	4
Small Lymph	24	21	15	27	4	26	11
Large Lymph	10	17	17	23	19	9	5
Mononuclears	10	6	5	4	8	6	5
Myeloblasts	..	..	..	..	..	..	4
Myelocytes	..	..	..	..	..	1	6
Metamy.	1	..	1	..	..	..	1
Band Cells	19	11	10	6	8	5	6
Non-S-shaped	9	2	7	4	15	3	7
Multilobed	11	22	32	24	27	23	21

permissible, either before or after death, of the bone marrow and spleen and hence the scientific data of the case remain incomplete and inconclusive and thus invite justifiable argument and conjecture regarding their nature.

Comment

The most striking feature of this case is the marked eosinophilia. According to Downey[6] eosinophilia frequently accompanies a great many diseases or disorders, some of which are: (1) parasitic infestations, like malaria, hookworm, trichinosis; (2) infectious diseases, as asthma, endocarditis, scarlet fever, rheumatic fever, intestinal tuberculosis, chronic colitis, Hodgkin's and Addison's diseases, leprosy, purpura, pyelitis and pneumonia; (3) dermatoses, like dermatitis herpetiformis, pemphigus, bulbous dermatitis, scabies, mycosis, fungoides and urticaria; (4) constitutional disturbances, such as, treated pernicious anemia, post-splenectomy, vagotonia, osteomalacia, polycythemia, gout; (5) malignant tumors; (6) drugs, like camphor, coal tars, gold, and toxic conditions due to foreign proteins.

It is reasonably certain that all the above conditions can be excluded in this case except the tuberculous colitis. That a tuberculous process of the intestines could become so severe and fulminating as to produce in the terminal three weeks of life an enlarged liver, an eonrmous spleen, and so active a myeloid reaction seems unlikely. Familial eosinophilia occurring not infrequently, as one notes from the excellent review of the literature and the report of eosinophilia in four families by Stewart,[16] was also eliminated. To maintain, again, that this was just an individual constitutional eosinophilia appears both groundless and defenseless.

Since hematologists today recognize the ability of a leukemia to develop from the primitive myeloid cell stems or elements that eventually appear either as the polymorphonuclear neutrophil, basophil, or eosinophil, the classification and determination of each kind of leukemia would be definite and indisputable if the basophilic and eosinophilic leukemias behaved like the neutrophilic type. Unfortunately the basophilic as well as the eosinophilic types of leukemia resemble, as Groat, Wyatt, Zimmers and Field[9] have shown, each other by keeping "toward the mature"—instead of the immature cell in the circulating blood "regardless of the company they keep." This is also true of the case under discussion. Nearly all of the eosinophils are mature. Most hematologists detest making a diagnosis of leukemia on predominantly or nearly exclusively mature cells, yet many admit the possibility that an eosinophil or basophil might well behave in such a manner and appear in the mature form in basophilic or eosinophilic leukemia. Some, therefore, are accepting reluctantly the diagnosis of eosinophilic leukemia, while awaiting a definite solution. Others again, prefer to designate such a condition as a myelogenous leukemia with eosinophilic hyperleukocytes or eosinophilic hyperleukocytosis with splenomegaly. The trend of medical writers, however, leans toward the retention of the designation of eosinophilic leukemia, at least, until there is a better understanding of this condition.

Brief Review of the Literature

Hays and Evans[11] in a masterly review of the subject of eosinophilic leukemia attributed the first report to Stillman[17] in 1912, under the title "Myeloid Leukemia with Preponderance of Eosinophil Cells." The subject was a man, aged 27, who showed an enlarged liver, spleen and cervical, inguinal and epitrochlear glands. The blood Wassermann was positive and the urine contained a trace of albumin and some casts. The white cells varied from 118,000 to 165,000 per c. mm. of which number 85 to 91 per cent were eosinophils (polymorphonuclear 69.8—metamyelocytes 19.4—myelocytes 1.8). It is stated that the eosinophils were larger than normal, but the granules somewhat smaller. What happened later to the patient is unknown. Giffin[8] studying a man, aged thirty-one, who complained of dyspnea and pain in the chest, found in addition to marked evidences of cardiac decompensation, a large liver, spleen, and axillary glands. The white count was 15,400, of which 66 per cent were eosinophils but myelocytes were very rare. After the removal of the spleen, which weighed 2,100 grams, the white count reached 208,000 in ten months and the eosinophils accounted for 79 to 90 per cent. After six years death ensued. The necropsy revealed a broncho-pneumonia, chronic pleurisy, obliterative pericarditis, fibrous perihepatitis, cirrhosis of the liver and a hyperplastic bone marrow. He concluded thus: "I am inclined to regard the case as an instance of eosinophilic hyperleukocytosis, the blood picture of which was remarkably altered by splenectomy." Shapiro[14] reported a man, aged forty-nine at death, with a five year illness, who had a large spleen and liver and palpably enlarged inguinal and epitrochlear lymph nodes. The Wassermann was strongly positive and the white count read 19,800 with 70 per cent eosinophils. In less than a year it reached 236,000 with 79 per cent eosinophils, most of which were of the adult type. Autopsy showed a large liver, and spleen, and cellular marrow with numerous eosinophils, both myelocytic and polymorphonuclear, also numerous myeloblasts. He, therefore, came to the conclusion that this was a case of leukemia arising in the eosinophil system of cells. Again in 1922 McDonald and Shaw[13] reported a man, aged forty-six, with digestive disturbances for several years' duration, who had a large spleen and white cell count of 34,000 with 71 per cent eosinophils. The removed spleen weighed 1,276 grams. Some fourteen months after the splenectomy, the white cell count had risen to 138,000 with 84 per cent eosinophils, of which around 98 per cent were the adult type and 2 to 8 per cent myelocytes. Sometimes basophilic granulations were mixed with the eosinophilic ones. The patient died within two years. No autopsy was done. The authors are inclined to view the case as more allied to leukemia than any other condition. Alexander[1] studying a man, aged forty-seven, five years after a splenectomy, noted marked asthenia, pronounced anemia and dyspnea. The spleen weighed 2.200 grams and had been removed for the anemia. While the blood count before the splenectomy was only 9,400 it was now 150,000 of which 24 per cent were eosinophils. Later the red blood count too

fluctuated between 1,200,000 and 4,300,000; the white count, between 19,000 and 70,000; and the eosinophils constantly averaged about 30 per cent. Necropsy showed a large liver and cellular bone marrow with many eosinophils. This case was considered to be an atypical form of myelogenous leukemia.

In 1925 Bass[3] reported an unusual eosinophilia with splenomegaly in a child aged six. Clinically she had rickets, but in addition the spleen, liver and cervical glands were enlarged. The blood showed: hemoglobin 80, red blood count 4,300,000, white blood count 25,000 of which 64 per cent were eosinophils. Death followed from a broncho-pneumonia in two months, but no autopsy was obtained. Evans and Hays[11] described in 1928 a case of acute eosinophilic leukemia in a man, aged forty-one, which the course of the disease ran to a fatal termination in less than three weeks. The eosinophils constituted over 83 per cent of the total white blood count of 72,187. A study of the eosinophilic cell showed 75.5 per cent polymorphonuclear, 3.8 per cent myelocytes, and 4.4 per cent metamyelocytes. Furthermore, they varied considerably in size and seemed to be larger than normal. The granules, too, varied in size. Sometimes they appeared larger than normal but at times they were very fine or almost totally absent in certain areas of the cytoplasm. At autopsy the bone marrow was found to be very cellular and the spleen markedly infiltrated with eosinophils as well as the lymph nodes and liver. They state, "It is curious that in this as in other reported cases, the eosinophils were mainly of the adult type, considering the acute nature of the disease (three weeks) this case seems unique in medical literature."

Harrison,[10] in 1930, reporting the case of a man, aged 33, who died of eosinophilic leukemia, called attention to the increased metabolic rate. The case showed a basal metabolism of plus 35 per cent and at autopsy in addition to the usual eosinophilic infiltration in all the organs contained multiple small hemorrhages in the lungs resembling tuberculosis. The white blood count averaged 13,000 to 16,000 of which 55 to 60 per cent were mature and one per cent immature eosinophils. Bass,[4] reporting a second case in a boy, aged eight, in 1931, found also an increased basal metabolism, namely, plus 31 to 48 per cent. The white blood cells in this case were also predominantly mature, ranging from 32 to 76 per cent in eosinophils in a count of 26,400 to 47,000. Bone biopsy showed myeloid hyperplasia. Stephens[15] reported a girl, aged seventeen, with severe petechial hemorrhages. An acute leukemic state became superimposed on a chronic form and the patient died in less than two weeks. The white blood count reached 130,000 of which 67 per cent were mature and one per cent immature eosinophils. Forkner's[7] case, a man, aged thirty-three, reported in 1937, developed after an extraction of an upper molar tooth, severe weakness, sore throat, listlessness, and hemorrhagic spots over the whole body. The platelets fell to 5,000 and the leukocytes ranged between 118,000 and 254,000 of which 75 to 81 per cent were eosinophils. The whole course of the disease ran less than a month. In the acute form of eosinophilic leukemia, the author states, the length of the disease runs from twelve days to three months.

Thomsen, Stig, and Plum[18] studied a boy, aged eleven, with eosinophilic leukemia which followed an acute tonsillitis. After radiation the spleen decreased in size and the white blood count fell from 65,000 to 5,000, of which 70 to 90 per cent were eosinophils. Eight months later, however, the gradual growing enlargement of the cervical glands was treated again by radiation. After a stationary four-month period myeloblasts appeared in the blood stream, mature eosinophils disappeared and the bone marrow showed no further stem cells. At autopsy a leukemic condition of the bone marrow was found. This case showed in the clinical course a transition from the typical eosinophilic leukemia to an entirely myeloblastic leukemia. The authors in discussing eosinophilic leukemia state: "Hematologically it is characterized by an enormous, absolute and relative increase in the number of eosinophilic granulocytes, but the dominating cell-form has a particular mature appearance, with a segmented nucleus and coarse granulation. On close examination these cells are found to differ considerably from the normal eosinophil granulocyte."—They are considerably larger, and the nuclei are more loose in structure than normally. The protoplasm is more abundant, and most often distinctly basophilic, the granules are abnormally large, and their number is far smaller than in normal eosinophils: and often the granules are heaped together in a single accentuated group. Histologically the bone marrow, spleen, liver, kidneys, and lymph glands show marked infiltration with eosinophilic granulocytes essentially of the same form as described above."

Broadly speaking laboratory studies and clinical observations point to wide variations not only in the course of certain white blood cells but also in the response of the blood-forming organs. One is almost forced to admit that under favorable conditions, any white cell, be it a lymphocyte, mononuclear, basophil, eosinophil, or neutrophil may decrease or even disappear from the circulation or again increase slightly, moderately or overwhelmingly either in mature, mixed, or immature forms. Thus, for example, the mononuclear cell might be leukopenic, hyperleukocytic, as in infectious mononucleosis, or leukemic as in monocytic leukemia. Whether or not the immaturity of the cell, to the total exclusion of the predominantly mature character of the cell with fatal termination of the case, should be the only guide in designating or classifying basophilic and eosinophilic leukemias remains still a debatable question. The tendency, however, seems to be to accept a case as eosinophilic leukemia, which has a white blood count very high in eosinophils, a large spleen, large liver and enlarged lymph glands with a fatal termination despite the largely or predominantly mature character of the eosinophil. Downey,[6] however, leans toward the acceptance, as myelogenous leukemia, of all the conditions showing immaturity of the polymorphonuclear cell in the blood stream, and a very actively increased cellular bone marrow, regardless of whether they make their appear-

ance through the eosinophilic, basophilic, or neutrophilic routes or systems.

Summary and Conclusions

1. A case of pulmonary and intestinal tuberculosis with a high eosinophilia extending over a period of three years is reported, terminating in the last three weeks of life with a large spleen, enlarged liver, fever, and an atypical bone marrow reaction suggesting, according to some hematologists, an eosinophilic leukemia and according to others a myelogenous leukemia with an eosinophilic hyperleukocytosis.

2. Emphasis is placed on the fact that basophilic and eosinophilic leukemias, if such exist, do not conform to the established and time-honored scientific prerequisites of a leukemia based exclusively on the immaturity of the cellular elements, since the eosinophils or basophils are predominantly mature.

3. A review of the reported cases in medical literature favors the retention of the nomenclature of eosinophilic leukemia, at least until adequate studies of scientific clarification either confirm, alter or reject this designation.

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Discussion

DR. E. K. GEER, Saint Paul: Inasmuch as I attended the patient to whom Dr. Lepak has alluded, for his tuberculosis, there are a few remarks I would like to make. In the first place, most tuberculous persons reveal no serious or marked blood changes. The most common blood finding in chronic pulmonary tuberculosis is hypochromic anemia of varying degrees, usually not marked. If it is marked, causes other than tuberculosis should be suspected. Of the serious blood dyscrasias, I have yet to see pernicious anemia in a tuberculosis individual. I recall one case of chronic lymphatic leukemia which developed in a patient at Pokegama Sanatorium who was doing a good job of controlling her tuberculosis. If the case presented this evening is a true myelogenous leukemia, it is the first one I have seen coexisting with tuberculosis.

This patient made very satisfactory progress with artificial pneumothorax for his lung tuberculosis, his left upper lobe being closed thereby. The usual regime for intestinal tuberculosis controlled his enterocolitis and after leaving the hospital he remained well until an apparent throat infection in September, 1939, for which Dr. Lepak attended him. From this episode he did not make a complete comeback although he was up and around. In October, when he came to my office for his monthly pneumothorax refill he looked washed out, so I gave him a general physical examination. At the time no enlargement of his liver or spleen was apparent but a change was noted in his blood picture, premature cells being evident. He returned in a few days at my request to have this checked and then was advised to have consultation.

The next thing I knew of him was after his last admission to the hospital. The dramatic downhill course has been described by Dr. Lepak.

The eosinophilia which was noted while he was being treated in the hospital for tuberculosis was unexplained. He certainly was suffering from none of the disorders commonly associated with an increase of eosinophils in the circulating blood. When he developed symptoms suggesting a tuberculous enterocolitis and substantiating evidence was forthcoming with a barium enema, I was inclined to explain the eosinophilia on that basis, having noted it in the literature but never having seen it in patients under my care either before or since.

DR. H. Z. GIFFIN, Rochester: I think Dr. Lepak would want me to say something about the case I reported in 1919 which proved to be the second case in the American literature. The patient in that instance showed a very marked eosinophilia of from 70 to 90 per cent and developed a severe leukemoid reaction following splenectomy. At postmortem examination, an extensive chronic infectious process was found involving the pericardium and the peritoneum. Cases similar to Dr. Lepak's case and mine have been reported in the literature and I believe it is most logical to regard this particular type of case as not falling into the group of true leukemias. However, in the literature one finds three types of cases: (1) cases of chronic type in which the eosinophilia seems to be secondary to some other process; (2) cases in which the condition begins very much as it did in Dr. Lepak's case and in which, later, there develops a true picture of leukemia with many myeloblasts in the blood; and (3) a type in which the process is of very short duration and an acute myeloblastic leukemia develops. Four or five of these acute cases have now been reported and I do not see how we can regard them as entirely secondary, especially in view of the high percentage of myeloblasts present and the short history which, in some instances, is only of a few weeks' duration. For the sake of argument at least, I am willing to say that there are also two types of cases of the more chronic condition, one type which develops a leukemoid reaction and the other which is a true leukemia.

DR. JOHN F. NOBLE, Saint Paul: This case of Dr. Lepak's has been very interesting to me, particularly so because about a year previous to this case, we had a somewhat similar experience. I am not at all convinced that there is such a thing as a true eosinophilic leukemia. I say that on the authority of Dr. Downey, and the statement is supported by my own experience. Several years ago we saw a patient, a man, aged 28, who stated that he had been well until six years before his admission to the hospital when he developed asthma following an attack of bronchitis. During the first year

the asthmatic attacks were infrequent and were associated with respiratory infections. A change in climate gave the patient a year when he was free from symptoms, but after a recurrence of his asthma a similar change in climate gave him no relief. The patient had been taken care of by a number of physicians and he had received all the usual types of therapy, including vaccines, calcium gluconate, adrenalin and ephedrine. Protein sensitivity tests were negative, and clinically it was felt that the patient had asthmatic bronchitis on an infectious basis.

The eosinophilia was first noted in October, 1937, at which time there was 10.5 per cent present. A careful study of the smears at this time showed no abnormality. His complaint at the time of his admission to Ancker Hospital was severe abdominal pain of such degree that at one time a laparotomy was considered. There was a palpable mass in the left side of the abdomen which was thought to be the spleen. Our blood studies showed as high as 77 per cent eosinophils. About 6 per cent of promyelocytes were observed, but these were the most immature cells seen, though many of the eosinophils showed changes which were interpreted as slight immaturity. These changes were a lack of typical staining characteristics of the eosinophilic granules.

Clinically this patient was considered as a possible eosinophilic leukemia and even at autopsy the infiltration of his organs suggested this diagnosis. More careful study, however, showed that the picture was that of a periarteritis nodosa and not a leukemia. The palpable mass in the abdomen proved to be a massive retroperitoneal hemorrhage from an aneurysm of a small renal artery.

In reviewing the literature of periarteritis nodosa and eosinophilic leukemia, the similarity in the sex distribution, the clinical symptoms and the blood picture in the two groups of cases was striking, and I wonder how many of the cases of so-called eosinophilic leukemia may be periarteritis nodosa.

Dr. Moses Barron, Minneapolis: This is a very interesting case that has been presented tonight and I am very glad Dr. Lepak reported it although I may disagree with his conclusions. An increased number of eosinophils is found in the blood of various conditions. In the foreign literature it is often reported that it is associated with some cases of tuberculosis. Loeffler described a syndrome of a peculiar spreading lesion in the lungs associated with an eosinophilia that ranged from 10 to 66 per cent. His cases were principally associated with tuberculous lesions and with asthma. In the case presented tonight it seems to me the blood picture did not show the presence of a sufficient number of myelocytes. Dr. Lepak stated that, although an eosinophilia had been present for several years, no promyelocytes, myelocytes or metamyelocytes were found until a month before death. One has to consider trichiniasis as a cause of eosinophilia. I do not believe that there is enough evidence in this case to consider it one of leukemia. It is difficult to state what was the actual cause of death. It is unfortunate that postmortem examination was not obtained. I would like to know how large the liver became, as well as the spleen. What was the blood picture at the time the diagnosis of leukemia was made?

Dr. Thomas J. Kenyon, Saint Paul (by invitation): An eosinophilia was first noted in this patient in December, 1937, at which time it was 15 per cent. Another blood study was made in the latter part of December 1937 and revealed an eosinophilia of 20 per cent. During 1938, the eosinophilia ranged from 15 to 18 per cent. On September 15, 1939, the patient's hemoglobin was 86 per cent, the white count 12,100, red count 4,465,000, the color index 0.97. A differential count revealed the polymorphonuclears to be 32 per cent, the eosinophils 25 per cent, basophils 2 per cent, lymphocytes 35 per cent, and the monocytes 6 per cent. Of the neutrophilic series alone, 1 per cent were myelocytes and 5 per cent of them were band cells. On December 1, 1939, the hemoglobin was 82 per cent and the white blood count was 40,300. The red count was 4,180,000 and the color index 1. The differential count revealed the polymorphonuclears to be 45 per cent, eosinophils 31 per cent, basophils 4 per cent, lymphocytes 16 per cent and monocytes 5 per cent. Of the entire granulocytic series, 4 per cent were myeloblasts, 6 per cent myelocytes, 1 per cent metamyelocytes and 6 per cent band cells.

As to the slides that were shown, slide I shows two eosinophils. Most of the eosinophils noted in this blood slide were of the mature type. Slide II shows a myeloblast with its narrow zone of cytoplasm and a few azure granules. The nucleus presents the typical sieve-like appearance with two nucleoli. There is an early nucleated red cell in this slide. Slide III is another myeloblast or stem cell. Slide IV shows a myeloblast and a leucoblast. There is also a basophil and neutrophilic metamyelocyte present. Slide V shows a promyelocyte and a neutrophilic metamyelocyte. Slide VI shows a nucleated red cell, basophil, a neutrophilic metamyelocyte and a neutrophil. Slide VII shows four eosinophils.

In studying blood slides made in September and December 1939 we thought that we were dealing with a myelogenous leukemia and did not attach any particular significance to the eosinophilia. It was also Dr. Downey's opinion, in the blood picture of these slides, that we were dealing with a myelogenous leukemia.

Dr. E. K. Geer: Apropos of Dr. Barron's remarks concerning a European report which dealt with eosinophilia in tuberculous patients, may I add that we must have a different brand of the disease in this part of the United States; one that doesn't stimulate eosinophil formation. I am sure Dr. Noble will bear me out in this statement at least as far as patients on the tuberculosis service of Ancker Hospital are concerned.

Dr. Lepak, in closing: I am very grateful for the generous discussion of this unusual condition. The reported case was intended to serve that purpose. So far as I am concerned, the case remains doubtful since we did not have a postmortem examination. Every one can think, therefore, as he pleases about its exact nature.

Dr. Barron: How large was the spleen? How much do you think it might have weighed? And how large was the liver?

Dr. Lepak: The spleen extended down below the left iliac crest and might have weighed about 2,000 grams. The liver was found to extend about one inch below the umbilical line.

HOUR-GLASS-SHAPED MENINGIOMA INVOLVING MEDULLA, FORAMEN MAGNUM AND CERVICAL REGION

George N. Ruhberg, M.D.,
Saint Paul, Minnesota

Hour-glass tumors although not rare are of sufficient infrequency that in many situations unless one has been conditioned to them by clinical experience or met them at the autopsy table their possibility is often overlooked.

They arise from the membranes, nerves, and ganglions of the spinal cord, from the sympathetic nervous system, from the ligaments in or about the verte-

bræ, from the cartilage of the auricular surfaces of the vertebræ and ribs and rarely from the epidural fat. The larger number have arisen from the membranes, nerves, and ganglions of the cord.

Their method of growth may be as follows:

1. Arising within the spine, growing outward and extending through an intervertebral foramen and enlarging again in the paravertebral structures.

2. Arising without the spine and progressing into the spinal space and enlarging.

3. Arising within the intervertebral foramina and growing in both directions.

4. According to Coenen these tumors take a passive and not an active part in determining their shape. They are present as tumors, possibly as spherical tumors, before the development of the skeleton, whose development impinges upon them and give them their shape.

The case presented tonight is that of a meningioma assuming an hour-glass-shape by springing from the medulla, passing through the foramen magnum and presenting as a mass in the posterior cervical region.

E. D. L., a colored boy of four years, was admitted to the Children's Hospital, Saint Paul, on January 1, 1940, because of stiff neck, pain in the neck on movements of the head, tilting of the head and a mass in the posterior cervical region. Present illness as stated by patient's uncle began two years ago after falling down stairs. Since that time he has carried his head turned to one side.

On physical examination, he was well developed and fairly well nourished, and in no acute distress or pain. Temperature was 100 2/5 rectally and varied from 99 to 100 degrees during hospitalization. He held his head tipped forward and rotated to the right side in a fixed position. On attempting to move his head from side to side he would turn his whole body. He cried when an attempt was made to passively turn, flex or extend the head. The cranial nerves and eye grounds were negative. There was some exudate in the nose. The throat was slightly injected. There was a large "cervical gland" on the right side behind the ear. This was hard and fixed. The lungs were clear. The heart was normal. The abdomen was essentially negative. The extremities showed normal reflexes. Movements of his head caused pain.

Laboratory studies of urine and blood were essentially negative. Wassermann and Mantoux tests were negative. Roentgenogram of the cervical spine was essentially negative. The chest showed moderate pulmonary congestion and bronchitis. The mastoids were negative. No definite diagnosis was made.

On January 27, 1940, a neurological examination by the writer revealed objective findings as follows:

1. Head held tilted forward and to the right.

2. Stiff neck and painful reactions on attempted movements of head.

3. Paresis of left upper extremity and diminished biceps reflex.

4. Sustained left ankle clonus and increased reflexes of left lower extremity.

5. Spinal fluid showed a cell count of 4 and total protein of 210 mg.

6. Sensory findings were not reliable on account of lack of coöperation of the patient.

A diagnosis of a central nervous system involvement of the upper cervical region was made and a biopsy recommended of the "cervical gland." On account of the rapid decline in the patient's physical condition this was not carried out. Paralysis spread to both arms and left leg by January 30 and he died February 1, 1940.

Necropsy findings were essentially unimportant with the exception of the findings relative to the lesion involving the neck and central nervous system.

A subcutaneous tumor mass resembling an enlarged lymph node was found in the posterior portion of the right neck just behind the ear. It measured 4 x 2.5 x 2 cm., and it was firmly attached to the border of the foramen magnum on the right side. On section, this tumor consisted of pale yellowish gray cellular tissue, which was soft and friable. Examination of the cortex was grossly negative. On lifting the cerebrum there was found a well encapsulated rounded slightly lobulated tumor measuring approximately 3 cm. in diameter and arising by a pedicle from the dura over the right anterior surface of the lower posterior portion of the medulla and completely occluding the foramen magnum and in so doing, displacing the medulla to the left and posteriorly and compressing it. On the right side this tumor infiltrated through the foramen and directly connected with the tumor in the neck. It consisted of soft, yellowish gray cellular tissue similar in character to that found in the neck tumor. A diagnosis was made of:

1. Meningioma of the medulla with extension into neck and compression myelitis of the medulla.

This case is an example of so-called hour-glass-or dumb-bell-shaped tumor of intracranial and cervical involvement, exhibiting the syndrome of tilting head and signs of compression myelitis described by Elsberg and others in cases of tumors involving the foramen magnum. Appreciation for the opportunity of examining this case is acknowledged to Dr. George Hagerman, on whose service the patient was, and to Dr. Kano Ikeda, who performed the autopsy and made the microscopical diagnosis.

Discussion

Dr. J. F. Noble, Saint Paul: I have nothing special to add to the discussion of this case. I have never seen a meningioma in a child of this age. From the lantern slides it seems to me that a diagnosis of meningioma is justified, and, since that was Dr. Bell's diagnosis, I can see no reason for doubting it.

The meeting adjourned.

A. G. Schulze, M.D., *Secretary.*

TRANSACTIONS of the MINNEAPOLIS SURGICAL SOCIETY

Stated Meeting, Thursday, December 7, 1939

President, DR. WILLARD D. WHITE, in the Chair
Secretary, DR. HARVEY NELSON

GASTROJEJUNAL ULCER FOLLOWING GASTRO-ENTEROSTOMY PERFORMED TWENTY-FOUR YEARS BEFORE FOR PYLORIC STENOSIS OF INFANCY

L. HAYNES FOWLER, M.D.
and
WILLIAM A. HANSON, M.D.
Minneapolis

This patient was a young man twenty-four years of age. He consulted us in June, 1938, on account of recurring attacks of epigastric pain accompanied by hematemesis and melena. He stated that he had had a gastro-enterostomy performed on account of pyloric stenosis when he was six weeks of age, i.e., in 1914. He grew to young manhood and had no symptoms relative to his stomach until six years ago, when he was eighteen years old. For the past six years he has had intermittent attacks of epigastric pain which were at first relieved by food, soda and an ulcer diet but which recently have become almost constant and much more severe. During these six years he has been hospitalized three times on account of severe bleeding, for which he has had several blood transfusions.

Physical examination was essentially negative. He was a well developed and well nourished young man. The abdomen was slightly tender to the left and above the umbilicus. Examination of his blood showed a moderate degree of secondary anemia.

X-ray examination of the stomach showed a large well-functioning gastro-enterostomy with a large area of ulceration on the jejunal edge of the stoma. Some of the barium could be forced through the pyloris.

A diagnosis of gastrojejunal ulcer was made and surgical treatment advised.

Operation was performed June 23, 1938, at Northwestern Hospital, under a general anesthetic. On opening the abdomen, a large opening from a posterior gastro-enterostomy was found. The pyloric outlet seemed smaller than normal, barely admitting the tip of the index finger. The stomach and duodenum were otherwise normal. The transverse mesocolon was dissected free from the posterior wall of the stomach, and the gastro-enterostomy taken down. There was a large necrotic ulcerated area on the proximal jejunal side of the stoma. This was excised, and the two large openings in the stomach and jejunum measuring four inches long were closed separately with two rows of chromic catgut reinforced with silk. A pyloroplasty was then done by making a longitudinal incision one and one-half inches long through the full thickness of the duodenum, pyloric muscle and stomach, and then suturing the same in a vertical direction, thus enlarging the outlet of the stomach. The abdomen was closed without drainage. The immediate postoperative condition was good. Continuous nasal suction was employed for four days. On removing the tube, the patient became very uncomfortable, the upper abdomen became distended and on reinserting the tube, 1500 c.c. of gastric retention was removed. After twelve days of temporizing, we felt satisfied there was complete obstruction, either at the pylorus or in the upper jejunum. The abdomen was re-opened. We found the pylorus in good condition. The loops of jejunum at and near the portion which had been detached from the stomach formed a mass of distended, red, obstructed bowel, adherent in a rent in the transverse mesocolon. We first attempted to free these distended loops but found this impossible. We then made an entero-anastomosis between the jejunum distal to the obstruction and the duodeno-jejunal angle. On account of the limited space, this was done without clamps. A number 14 French catheter was inserted into the jejunum distal to the anastomosis for feeding. Following this second operation, he still continued to have considerable gastric retention. Fluid injected into the jejunostomy tube was recovered from the stomach and vice versa. A flat plate of the abdomen showed the catheter to have passed through the entero-anastomosis and extended into the transverse part of the duodenum. The catheter was removed. The gastric retention ceased, and the patient made a good recovery. A normal diet was gradually resumed, and on leaving the hospital on August 3, 1938, he was eating everything without discomfort.

An x-ray examination after the ingestion of a barium meal on November 11, 1938, showed a slight narrowing in the middle third of the stomach. The barium passed freely and rapidly into the jejunum, which had been obstructed, and also through the entero-anastomosis. Plates taken two and one-half hours later showed the stomach empty, the head of the column at the transverse colon and the tail in the lower ileum.

The patient has remained well and free from any gastric symptoms to date, which of course is only one and one-half years.

Comments

This case has several interesting features:

The first is that this six-weeks-old baby survived a gastro-enterostomy performed for pyloric stenosis. This operation was done in 1914 by a Saint Paul surgeon, name unknown, two years after Rammstedt first reported his well-known operation for pyloric stenosis.

Secondly, in a limited review of the literature we have been unable to find another reported case of a gastrojejunal ulcer forming in a gastro-enterostomy stoma performed for pyloric stenosis.

Third, the opening between the stomach and jejunum was unusually large (four inches long). Apparently the opening grew as the boy developed.

Fourth, as a result of the large stoma, there was very little tissue in the transverse mesocolon to close, which undoubtedly contributed to or caused, the postoperative obstruction.

Fifth, the essential surgical treatment consisted of disconnecting the gastro-enterostomy. It is well known that an ulcer of the stoma will heal if only this is done. Usually, gastrojejunal ulceration follows a surgical procedure done for the relief of a peptic ulcer. Such a situation ordinarily necessitates a partial gastrectomy in addition to taking down the gastro-enterostomy. In the case reported, we had no antecedent peptic ulcer. We therefore felt that a pyloroplasty was more indicated and performed the same. Time will tell whether or not our judgment was correct.

LEIOMYOSARCOMA OF THE ILEUM*

RALPH EMERSON WEIBLE, M.D.
Fargo, North Dakota

Mr. E. C. M., aged sixty-four, was a farmer weighing 200 pounds and had been well until his present complaint. He came to the hospital June 18, 1939, at 2 P. M., stating that he had fallen ill sixty-four hours previously with a severe chill and acute generalized abdominal pain. The pain subsided somewhat after a half hour and he did not go to bed. The persisting soreness seemed to him to be centered just below the umbilicus. He took no food. The day before admission he took a laxative and the bowels moved twice. At 8 P. M. he vomited. This was repeated at 3 A. M. Severe pain started again two hours before examination.

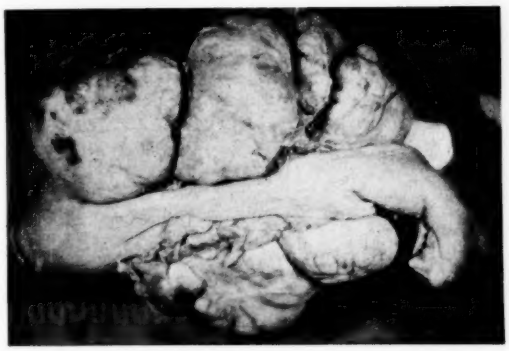

Fig. 1.

On examination the abdomen was distended and hard. No masses could be felt but it seemed he was more tender below the umbilicus. His blood pressure was 140/80, temperature 100, pulse 110. Three hundred c.c. of dark fluid were removed from his stomach. X-ray showed no free air under the diaphragm.

Under spinal anesthesia the abdomen was opened to the right of the midline. There was considerable dark, foul smelling fluid. No lesion was found in the epigastrium. A large tumor of the ileum situated below the umbilicus was brought into the wound. There was a perforated, gangrenous area in the tumor. The intestine and tumor were excised and an anastomosis of the bowel done. Fluid was aspirated and the wound closed with a drain. The patient, after a succession of complications from peritonitis, died three weeks after operation.

Leiomyosarcoma of the small intestine may be truly malignant or very mildly malignant in character. The truly malignant type are relatively small, seem to grow from the inner muscular layers, and tend to grow into the lumen of the bowel.

The mildly malignant type are large tumors projecting out from the bowel. It would seem that they grow from the outer longitudinal muscle. If operated upon before perforation occurs, the outlook is good.

A few case reports from the literature were abstracted and the subject discussed.

*From the Dakota Clinic.

CONGENITAL CYSTS AND FISTULÆ OF THE NECK

ARNOLD SCHWYZER, M.D.
Saint Paul, Minnesota

A most interesting and instructive description of branchial cleft or lateral neck cysts and fistulas and thyroglossal cysts and fistulas was given by Dr. Arnold Schwyzer of St. Paul by invitation. A very complete description of the embryology, diagnosis and treatment of these conditions was given in Dr. Schwyzer's usual thoroughness and detail. Numerous illustrative slides were presented.

Discussion

DR. MARTIN NORDLAND: It has been very pleasant and enlightening to listen to Dr. Schwyzer. He has been called upon often by Minneapolis medical societies and he always has brought something of interest and value to us. His splendid and complete presentation of this subject tonight has demonstrated how important it is to have a thorough understanding of the embryological development and the anatomy of the neck in order that one may properly diagnose and treat these lesions. Most of us have encountered cases of this nature in which the proper diagnosis was not made and as a result of this, inadequate treatment was rendered.

Dr. Schwyzer did not comment on the incidence of congenital cysts and fistulæ of the neck. In a recent article from the Lahey Clinic published in the *A.M.A. Journal*, it was reported that only .05 per cent of the total number of registrations at that clinic in a period of fifteen years from 1921 to 1936 were so classified. From the Jackson Clinic at Madison, Wisconsin, Dr. Arnold Jackson recently reported thirteen cases of lateral branchiogenetic cysts encountered over a period of ten years. Cattel in a recent discussion of this subject, called attention to the infrequency of the occurrence of thyroglossal duct anomalies, by the statement that they are found to exist at a ratio of 1 to 90 as compared to thyroidectomies.

It is obvious therefore, that while the occurrence of these lesions is not rare, nevertheless, it is evident that they are encountered so seldom in the experience of the average surgeon that they are not always recognized. As a result, the proper treatment is not always administered.

It is readily seen from Dr. Schwyzer's description of these lesions that the surgical treatment must be carefully planned and executed. While it may be considered elementary, still I think it is worthy of attention that the patient should be carefully placed in good position before the operation is started. Dissection of fistulous tracts and the removal of adherent scars can then be better accomplished without accident. I was very happy to hear Dr. Schwyzer call attention to, and recommend a transverse incision. Incisions along the anterior border of the sterno-mastoid always leave ugly scars. They were abandoned years ago in the surgery of the thyroid and should never be used in any surgery of the neck. Excellent and adequate exposure for the removal of congenital cysts and fistulæ of the neck is obtained through the transverse incision.

DR. E. T. BELL: These tumors are interesting chiefly because of their rarity. This tumor is of low malignancy, barely coming into the group of sarcomas. I think the diagnosis is justified here because of the mitoses and because the tumor was steadily getting larger. The leiomyomas in the intestine as well as those

in the stomach and other situations seldom form metastases. I have only one record of a metastasizing leiomyosarcoma.

It is of interest that the myomas of the uterus which are histologically malignant, are clinically benign. We have uterine myomas with four or five mitoses per high powered field, which were cured by hysterectomy or even by myomectomy. Some of the five-year cures look very malignant histologically. In the uterus the diagnosis of leiomyosarcoma doesn't seem to carry an unfavorable prognosis with it and it doesn't demand any treatment other than what you give to a simple benign myoma.

The myomas of the stomach are of interest. I have seen two very large intralumenal myomas of the stomach. One of these had a rather interesting history. A little over ten years before the patient died, he sustained a very severe burn. Some months later he developed gastric symptoms and a diagnosis of carcinoma of the stomach was made. That diagnosis was confirmed by the best men around town; roentgenologists, as well as surgeons thought it was carcinoma of the stomach. It was maintained that the burn caused an ulcer and that the ulcer developed into a carcinoma. The man was paid compensation but he refused to die of the carcinoma—in fact, he lived for ten years. Ten years after he was awarded the compensation, he died from a perforation of the stomach. The myoma filled the stomach completely and was of enormous size. There was just a little rim of space left in the stomach around the tumor. The tumor extended the whole length of the stomach and had caused an ulceration through the wall. The pressure on the stomach caused a perforation with peritonitis.

The other case of intralumenal myoma of the stomach also ended in perforation after several years. Extralumenal tumors are quite another matter. In the stomach they produce large masses that push the stomach from the outside and one can readily recognize that there is a tumor outside the stomach.

Dr. O. J. Campbell: A few years ago I had an experience with such a case which indicated that it might be difficult for the pathologist to differentiate between a benign leiomyoma and a leiomyosarcoma. This patient was an elderly man, a little past middle age. He came in with an acute abdomen. He had a tender mass in the left upper quadrant. I do not recall what our diagnosis was but needless to say, we were not accurate in our diagnosis. We went in and found and resected a leiomyoma about five inches in diameter, in the very first portion of the jejunum. It had not perforated but was covered by fiber and there was a localized peritonitis around it. I found no evidence of metastases. We resected the tumor mass. The man made an uneventful convalescence. Dr. McCartney, pathologist at Abbott Hospital, studied the tumor and thought it was probably a benign tumor and diagnosed it a leiomyoma. Approximately three years later, this man returned with a large mass in his right upper quadrant. There were no inflammatory elements about it. We watched it for a while and decided the only thing we could do was to do an exploration biopsy to see if there was anything that might help. We did this and found a tumor mass about the size of the patient's head adherent to the under surface of the liver. I found no other tumor masses in the abdomen nor the liver. A section of this was taken and was found to be hemorrhagic and necrotic. Dr. McCartney studied it and made a diagnosis of sarcoma. So the tumor we had operated on and diagnosed a leiomyoma should properly have been diagnosed a leiomyosarcoma.

BOOK REVIEWS

Books listed here become the property of the Ramsey, Hennepin and St. Louis County Medical libraries when reviewed. Members, however, are urged to write reviews of any or every recent book which may be of interest to physicians.

BOOKS RECEIVED FOR REVIEW

Modern Dermatology and Syphilology. S. William Becker, M.D., Associate Professor of Dermatology and Syphilology, Kuppenheimer Foundation, University of Chicago; and Maximillian E. Obermayer, M.D., Assistant Professor of Dermatology and Syphilology, Kuppenheimer Foundation. 871 pages. Illus. Price, $12.00, cloth. Philadelphia: J. B. Lippincott Co., 1940.

Clinical Diabetes Mellitus and Hyperinsulinism. Russel M. Wilder, M.D., Ph.D., F.A.C.P. Professor and Chief of Department of Medicine, Mayo Foundation for Medical Education and Research, University of Medicine; Head of Section on Metabolism Therapy, Mayo Clinic, Rochester. 459 pages. Illus. Price, $6.00, cloth. Philadelphia: W. B. Saunders Co., 1940.

Directory of Medical Specialists. Certified by American Boards, 1939. Paul Titus, M.D., Directing Editor. 1573 pages. Price, $5.00, buckram binding. New York: Columbia University Press, 1940.

The Relativity of Reality. René Laforgue, M.D. Translated by Anne Jouard. 92 pages. Price, $2.50, stiff board cover. New York: Nervous and Mental Disease Publishing Co., 1940.

Diseases of the Digestive System. A Text-book for Students and Practitioners. Eugene Rosenthal, M.D., Lecturer in Medical Faculty, Royal Peter Pazmany University, Budapest. Preface by R. J. V. Pulvertaft, M.D., F.R.C.P. Reader in Pathology. University of London: Director of John Burford Carlill Laboratories and Curator of Museum, Westminister Hospital School of Medicine. 394 pages. Illus. Price, $8.50, cloth. St. Louis: C. V. Mosby Co., 1940.

The Bacteriology of Public Health. George M. Cameron, Ph.D., Associate Professor of Bacteriology, University of Tennessee. 451 pages. Illus. Price $3.50, cloth. St. Louis: C. V. Mosby Co., 1940.

CANCER OF THE COLON AND RECTUM, ITS DIAGNOSIS AND TREATMENT. Fred W. Rankin and A. Stephen Graham. 358 pages, 210 illustrations in 133 figures. 54 tables. Price $5.50. Springfield, Illinois: Charles C. Thomas, 1939.

This volume is the most complete review of the subject of colonic malignancy published to date. While the whole tone of the book is authoritative, it is in the chapters dealing with "Choice of Operations and Operative Mortality and End-Results," that the authors are at their best. An operative mortality of 7.5 per cent for combined abdomino-perineal resection for cancer of the rectum and rectosigmoid is an achievement. However, it will be interesting to note if there will be any difference in the number of five-year survivals following abdomino-perineal resection and posterior excision for carcinoma of the rectum below the peritoneal reflection. For the surgeon who only occasionally operates upon such patients, colostomy followed by posterior excision is certainly the safer operation and would seem to be the procedure of choice.

Some may not agree with the statement that hernia-

tion is prone to occur after transverse colostomy (page 268); others may not believe that there is such a close correlation between histologic grading of colonic tumors and prognosis. However, the general excellence of the book overshadows any of these minor differences of opinion. The volume is strongly recommended for all interested in the subject of colonic malignancy.

—CHARLES E. REA, M.D.

THE MEDICAL CAREERS. Harry Cushing, M.D., Boston: Little, Brown and Co., 1940. An Atlantic Monthly Press publication.

In this volume is assembled a number of addresses and biographies, which have appeared in print elsewhere. The idea apparently is to publish these heretofore scattered products of the pen of a great surgeon in a single volume accessible to those who appreciate greatness, for Harry Cushing was not only a leading surgeon of his time but a fine character and an able writer. The material was selected for publication by the author and the editor of the *Atlantic Monthly Press* last summer, not long before Dr. Cushing's death. One would expect that the volume would be read with interest by all medical men, the younger ones particularly.

C. B. DRAKE.

OPERATIVE ORTHOPEDICS. Willis C. Campbell. 1154 pages. Illus. $12.50. St. Louis; C. V. Mosby Co., 1939.

This book offers an exhaustive description of procedures used in orthopedic surgery. It is well illustrated. Perhaps the only criticism one could offer would be the lack of critical analysis of the results of many of the operations here represented.—S.W.S.

CANCER HANDBOOK OF THE TUMOR CLINIC —Stanford University School of Medicine. Edited by Erick Liljencrantz, M.D. 114 Pages with fifty figures. Price $3.00. Stanford University, California: Stanford University Press, 1939.

This manual is a syllabus on the diagnosis and treatment of malignant tumors, assembled for postgraduate instruction at the Stanford University School of Medicine. In the first chapter, the cancer problem is stated simply, yet comprehensively. Diagnosis, treatment, and prognosis of the more frequent tumors are discussed. The diagrams are excellent, but the photographs of the lesions would be more effective if they were in color. The bibliography of the more pertinent literature is appended. The index is workable and fairly complete. This volume is one of the best handbooks on the cancer problem published to date.

—CHARLES E. REA, M.D.

STANDARDS FOR THE DIAGNOSIS AND TREATMENT OF CANCER. Cancer Manual developed by the Executive Cancer Committee of the Iowa State Medical Society. 168 pages. Price $1.00. Iowa City Iowa: Atheas Press, 1938.

The Iowa State Medical Society is to be congratulated on the publication of this splendid manual. It is almost incredible that so much regarding the symptomatology, diagnosis, and treatment of the more common tumors could be presented in this small volume. One may wonder if the authors are not a bit optimistic regarding the prognosis of cancer of the tongue (page 30). However, as a whole, the book is conservative, up-to-date, and practical. This manual could be read with profit not only by general practitioners, but also by all interested in the cancer problem.

—CHARLES E. REA, M.D.

ESSENTIALS OF THE DIAGNOSTIC EXAMINATION. John B. Youmans, M.D., B.A., M.S., Associate Professor of New York: Commonwealth Fund, 1940. Price, $3.00.

The book "Essentials of the Diagnostic Examination" by John B. Youmans, M.D., should prove a valuable addition to the library of the clinician. Physicians are always eager and thirsty for information that might help in diagnosis.

This compact book is divided into three parts. The first portion is concerned with the clinical history. The author in his introduction states quite clearly "The importance of the history or anamnesis can scarcely be overemphasized though, as stated in the introduction, no part of the diagnostic examination can be said to be more important than another. The reason for stressing the importance of the history is that it is so frequently neglected." This appeal in history taking should stir the practitioner who may feel that being pressed by time he finds it difficult to carry out this important procedure.

Also in part one of the book, Dr. Youmans discusses the physical examination, but the space devoted to this subject is limited. One finds many of the essentials hurriedly covered and inadequately described. The author has many references, however, to more complete works on this subject. On page 122 the author refers to a saying that "A medical specialist differs from a non-specialist in that he looks at the eye grounds and examines the rectum." This should, indeed be a challenge for more general practitioners to use the methods of specialists, and for more specialists to be specialists.

The section on the neurological examination should prove especially appealing to the general practitioner, the internist, and the surgeon alike. This section is opened by the statement that "Many physicians have a feeling of inadequacy with respect to neurology and neurological diseases. This is altogether unnecessary." With this challenge, Dr. Youmans goes on to lay down a sensible, practical, and clear method for the examination of the cranial nerves, reflexes, sensation and the mental state. The particular section should encourage the physician who altogether too frequently has regarded this portion of a physical examination as something obscure, and beyond his capabilities. Dr. Youmans' plea in this connection should not go unheeded.

In the second part the doctor discusses laboratory tests that are essential and commonly used. This section is well illustrated and the procedures are simply and very adequately described. The description of laboratory procedures is indeed timely in that the tests

for sulfanilamide and sulfapyridine blood determinations are well outlined. The doctor in practice who does his own laboratory work should be refreshed by this section.

There is nothing particularly new in this book. As the cover flap states, "This handbook sets forth procedures of the diagnostic examination that are essential to all good medical practice." The hand book follows the usual orthodox clinical and scientific plan and should be helpful in the performance of the important history taking, complete physical examination, and pertinent laboratory procedures. The hand book is adequately illustrated and indexed, and has numerous diagnostic charts that should be of help.

—Simon G. Sax, M.D.

AN INTRODUCTION TO GASTRO-ENTEROLOGY (The Third Edition of The Mechanics of the Digestive Tract). By Walter C. Alvarez, New York, Paul B. Hoeber, Inc., Medical Book Department of Harper and Brothers. 778 pp. Price $10.00.

To those who so thoroughly enjoyed the first two editions of The Mechanics of the Digestive Tract, this new volume should provide many evenings of delightful and thought-producing reading. In addition it is a veritable encyclopedia of fundamental and historic contributions to the physiology of the digestive tract, containing a bibliography of around 2,500 titles. This bibliography alone is worth the price of the volume, as a reference source.

The first few chapters describe the various types of motor functions of the small bowel and particularly the polarity of the bowel which waves travel more easily caudad than orad. The author and others have shown that there is a downward gradation in activity, tonus, irritability and rate of rhythmic contraction along the small bowel from the duodenum to the ileocecal sphincter (the "gradient theory"). These gradients constitute the best approach to the study of the polarity of the bowel. Other gradients have also been demonstrated, such as those of oxygen consumption and catalase content, blood supply, propulsive force, and pH of intestinal contents in many animals. Many factors tend to reverse or steepen these gradients. Flattened or reversed gradients are found in sick animals and in pregnant women, from emetics, or with rectal irritation even from use of a Murphy drip. Steepened gradients may be found from certain cathartics or from increased tonus in the upper end of the bowel due to ingestion of food. Bayliss and Starling's old "law of the intestine" is challenged, and the author proposes a new "law of the intestine" to the effect that any stimulus which raises the tonus, activity and irritability of a segment of bowel tends to slow the progress of waves and material approaching the segment on the oral side and to hurry the progress of material leaving on the caudal side. Reverse peristalsis may be a manifestation of an altered gradient in some segment of the bowel, and results in symptoms such as nausea, heartburn and bloating.

The next few chapters consider the structure of the smooth muscle and its nerve plexuses and their relationship to the extrinsic nerves of the digestive tract. The opinion is expressed that impulses from the extrinsic nerves are transmitted to smooth muscle of the bowel largely through chemical substances formed at the ends of the nerves. The rhythmic activity of the bowel is influenced by the extrinsic nerves yet its origin is in the bowel. The function of the myenteric plexus is to expedite conduction and to correlate activities of the muscle fibres. The ganglion cells of the plexus probably function to prevent the muscle contracting into a knot and remaining that way (as in cardiospasm, and Hirchsprung's disease). The effects of extrinsic nerve stimulation are not constant—they vary with the strength of stimulus, rate of interruption, and the level of tonus of the muscle at the moment. Afferent stimuli reach the brain and may harm the animal. Thus an animal with an obstructed overly active jejunum will live longer if the obstructed segments are denervated. The author discounts the old theory of a conflict between vagus and sympathetic—they both act to restrain excessive activity of the bowel. The vagus nerves have more to do with functions of the stomach and the splanchnics more with the bowel. Both, however, influence all parts of the small intestine. The vagus reaches only the proximal half of the colon. The quieting of the bowel seen in peritonitis is largely due to nervous inhibition, being much less marked in animals previously subjected to splanchnicotomy.

The cardia, pylorus and its control, and movements of the stomach are discussed in the next four chapters. There is no specialized cardiac sphincter in man, but only a variable amount of sphincteric action at the cardia. Such a sphincter is not needed in upright animals but is very pronounced in animals hanging upside down. The vagus and sympathetic nerves have varying effects on the cardiac end of the stomach depending largely on its tonus at the time of stimulation. Cardiospasm may often be due to separation of the muscle from its ganglion cells. Gastric contraction waves usually seen beginning near the middle of the stomach arise as ripples at or near the cardia, passing on down and resulting in a systole of the circular muscle of the antrum about three times each minute. More important for emptying the stomach are the slow tonic contractions of the whole muscular wall increasing the intragastric pressure. There is a mechanism present for adjusting the tonus of the gastric wall to the quantity of food taken. Indigestion arises if one eats too rapidly to allow this mechanism to function. The stomach muscle also has a "gradient" of irritability and contractility, greatest at the cardia. The author emphasizes the almost complete separation of pyloric and duodenal muscles, lymphatics and blood vessels. Animals and man live comfortably after removal of the pylorus for gastric emptying still is chiefly regulated from the bowel. One must remember that gastric waves do not push fluids through the pylorus. Many waves cause no emptying at all of the stomach. Only with increased intragastric pressure or relaxation of the duodenum does the stomach empty. The presence of food or liquid in the duodenum, regardless of

its acidity, retards gastric emptying. Likewise distention or irritation of the lower small bowel may delay gastric emptying. Fat in the bowel slows gastric emptying. Hydrochloric or other acids in the duodenum slow gastric evacuation by increasing intraduodenal tension. Alvarez sums up the controversy over the acid-control of the pylorus by calling acid control of the pylorus unimportant, since any substance, acid or alkaline, which increases the tonus of the gastric muscle and thereby the pressure within its cavity, must tend to speed up emptying. Any substance so acid or alkaline as to irritate the duodenal mucosa will be held back in the stomach until diluted or neutralized. In addition, the pylorus acts as a small funnel passing liquids but not solids larger than its bore. Duodenal contents regurgitate into the stomach if intraduodenal pressure is increased over that in the stomach. Fear, anxiety, pain or anger often slow gastric emptying for hours. The latter is speeded by lying on the right side or by exercise after a meal.

Two chapters are devoted to the movements of a diseased stomach and to the question of ulcer pain and hunger contractions. Most evidence points to the cause of ulcer distress as being irritation by the hydrochloric acid of the gastric juice rather than merely the contraction of the muscle overlying the ulcer. One problem yet unsolved is why some patients may lose all ulcer distress on the morning of the first day of their vacation. The author mentions the damage done to an ulcer during the night hours, and suggests the value of night neutralization of acid in the stomach. A periodic increase in the sensitiveness of the stomach or nervous system is important in explaining why ulcer pain appears at certain times. An ulcer anywhere in the stomach or duodenum may cause a hypertonic pars pylorica and thus delay gastric emptying.

The final third of the book is devoted to an unrelated group of subjects, such as vomiting, mechanics of the gallbladder, the appendix, movements of the colon, the length of the bowel under varying conditions, constipation etc.

Vomiting and diarrhea may often be associated due to emptying of the small bowel both ways from some midpoint which may be stimulated through the vagus nerves. The author emphasizes the fact that since the small bowel is more sensitive than the stomach to the nauseating effect of irritant drugs, putting such drugs in keratin or salol coating is irrational.

Present-day evidence is that emptying of the gallbladder is under the control more of a hormonal than a nervous mechanism. Decided slowing of emptying is seen after the third month of pregnancy. In emotional persons a temper tantrum may initiate an attack of gallstone colic. Colic seen in the absence of gallstones may be due to biliary dyskinesia or to failure of the sphincter of Oddi to relax with contraction of the gallbladder.

The ileocecal sphincter is not essential to good health—a simple anastomosis between ileum and colon is as satisfactory. Putting food into the stomach causes a hurrying of the residue from the ileum into the colon. Alvarez concludes that there is no pathognomonic

roentgenologic sign of chronic appendicitis. No correlation can be established between the x-ray findings on a supposed chronic appendix and the pathologists report on it after removal, for almost all appendices show slight evidence of past infection. The final test of the value of removal of a chronic appendix is to wait over a year to see if the operation cured the patient's symptoms. Improvement noted soon after surgery in these cases is often transient.

One of the main purposes of the colon is to conserve the water supply of the body. Constipation often is due to too great efficiency of the colon in removal of water from the bowel. Constipation is decidedly a disease of nervous origin—of civilization with its hurry, strain and tension. It may often be caused by too little food or too little residue in the food used. The results of stimulation of the colonic extrinsic nerves has not yielded clear-cut results. Children with megacolon usually are benefited by section of the nerves belonging to the lumbar sympathetic outflow.

The bowel in herbivorous animals is always much longer than that found in carnivorous animals. A rough indigestible diet will increase the length of the bowel in experimental animals and probably in man. In a living man the distance from mouth to anus is about 2.5 meters. In death this distance is two or three times as great.

It must be realized that a barium meal is not physiological. It passes through the bowel much faster than does most food. In normal young people colored glass beads require several days to a week for their passage through the digestive tract. The taking of much water washes food rapidly through the small bowel. This is often undesirable and results in indigestion and insomnia, and often diarrhea. Frequent feedings speed passage through the small bowel. Each new feeding gives a forward push to the residues of the preceding meal. Milk gives a bulky residue in the lower ileum and colon. Foods giving the least residue are lean meat, rice, hard boiled eggs and sugar.

Gas in the bowel consists largely of nitrogen remaining from swallowed air. In intestinal obstruction the gas also consists largely of nitrogen. Carbon dioxide leaves the bowel by diffusion most easily of all the gases found there. Oxygen is next and nitrogen is the slowest to diffuse into the blood. Breathing pure oxygen lowers the nitrogen tension in the blood and thus the nitrogen in the bowel may be taken up by the blood more easily. There is no gas produced in the stomach by fermentation, as is the case in the right half of the colon. Heart disease, allergy and protzoan parasites are all important causes of flatulence. "Gas pains" after operation are rarely due to gas.

The hunger complex is still not entirely clear. It is not due entirely to contractions in the stomach or intestine, or to a lowered blood sugar.

In doing a gastro-enterostomy it is not essential that peristaltic waves travel in the same direction in the stomach and the attached loop of bowel. Closure of the pylorus is apt to decrease the stimulus in the duodenum to the flow of bile and pancreatic juice and thus impair digestion. An entero-enterostomy increases the incidence of postoperative jejunal ulcer by removing much of the protective action of alkaline duodenal juices from the new stoma.

Two valuable chapters bring this book to its conclusion: one describing various technical methods and apparatus, and one containing advice to a young physician on his choice of books and reading. These are followed by the tremendous bibliography used in connection with the writing of this volume. This last chapter is characteristic of the charming and human personality of the author. Those who have heard Dr. Alvarez deliver a lecture will never want to miss an opportunity to hear him again. For those who cannot hear him, this book will provide a fund of information and an insight into the mind and personality of one of the greatest physiologists and clinicians of our time.

—J. Allen Wilson, M.D.